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# Anti-PD-1/PD-L1 immunotherapy in patients with solid organ transplant, HIV or hepatitis B/C infection

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Conflict of interest statement

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## Abstract

**Background:** Anti-programmed cell death protein 1/programmed death ligand 1 (PD-1/PD-L1) immunotherapy is now routinely used to treat several cancers. Clinical trials have excluded several populations, including patients with solid organ transplant, HIV infection and hepatitis B/C infection. We examined the safety outcomes of these populations treated with anti-PD-1/PD-L1 treatment in a multicentre retrospective study.

**Methods:** Patients from 16 centres with advanced cancer and solid organ transplant, HIV infection or hepatitis B/C infection were included. Demographic, tumour, treatment, toxicity and outcome data were recorded.

**Results:** Forty-six patients were included for analysis, with a median age of 60 years, and the majority of patients diagnosed with melanoma (72%). Among six patients with solid organ transplants, two graft rejections occurred, with one resulting in death, whereas two patients achieved partial responses. There were four responses in 12 patients with HIV infection. In 14 patients with hepatitis B, there were three responses, and similarly, there were three responses in 14 patients with hepatitis C. There was no unexpected toxicity in any viral infection group or an increase in viral load.

**Conclusion:** Patients with HIV or hepatitis B/C infections treated with anti-PD-1/PD-L1 immunotherapy may respond to treatment without increased toxicity. Given the risk of graft rejection in solid organ transplant patients and also the potential for response, the role of anti-PD-1/PD-L1 immunotherapy needs to be carefully considered.

**Keywords**

PD-1; Immunotherapy; Cancer; HIV; Hepatitis B; Hepatitis C; Organ transplant

## 1. Introduction

The use of anti-programmed cell death protein 1/programmed death ligand 1 (PD-1/PD-L1) checkpoint inhibitors in the treatment of cancer has substantially broadened in scope over the past few years. Originally shown to have high response rates and improve survival in advanced melanoma [1,2], subsequent trials across multiple cancer types have also shown benefit, such that anti-PD-1/PD-L1 inhibitors are now standard therapy for many cancer patients [3–8].

The PD-1/PD-L1 axis is known to play a pivotal role in immune tolerance, with PD-1 expressed on activated T cells and PD-L1 expressed on a large range of normal tissue [9]. Mice lacking expression of PD-1 have a higher risk of developing autoimmune cardiomyopathy and a lupus-like syndrome [10,11], while there is emerging evidence that certain PD-1 polymorphisms in humans may increase the risk of autoimmune conditions [12]. The PD-1/PD-L1 axis also plays a role in chronic infection and organ transplant tolerance, with PD-1 upregulation associated with T cell exhaustion phenotypes in chronic HIV and hepatitis B and C [13–15] and multiple animal models indicating that an intact PD-1/PD-L1 axis is required for transplant tolerance [16–18].

The major trials of anti-PD-1/PD-L1 inhibitors have excluded a number of specific patient populations, including those with autoimmune conditions, solid organ transplants and chronic viral infections such as HIV and hepatitis B/C, yet these patients are at greater risk of developing cancer [19–21]. Recent evidence indicates that selected patients with pre-existing autoimmune conditions can be safely and effectively treated with anti-PD-1 therapy, with mild and reversible flares of their underlying condition [22–24].

Approximately 30,000 patients receive solid organ transplants each year in the United States of America alone [25], whereas 1.2 million have HIV [26], 730,000 have hepatitis B [27] and 3.5 million have hepatitis C [28]. Many of these patients will be diagnosed with cancers that may respond to PD-1/PD-L1–based immunotherapy. Whether these patients can be safely and effectively treated with these therapies is unclear, with current evidence largely based on individual case reports, case series or small early-phase trials [29–31]. We therefore sought to explore the outcomes with anti-PD-1/PD-L1–based immunotherapy in these populations in a multicentre retrospective study.

## 2. Methods

The study was performed with institutional ethical review board approval. Patients with advanced cancer and concurrent solid organ transplant, HIV, hepatitis B or hepatitis C infection who were treated with anti-PD-1–or PD-L1–based therapy between July 2014 and March 2017 were retrospectively identified from 16 centres.

Data collected included demographics, cancer details (subtype, stage and performance status), underlying disease factors (condition, viral load, CD4 count and organ function), concurrent immunosuppressive or antiviral therapy at treatment commencement and immunotherapy treatment.

Conventional immune-related adverse events (irAEs) were assessed by the Common Terminology Criteria for Adverse Events (CTCAE), and details of any change in underlying condition, treatment required and outcome were collected. Response to treatment was assessed by Response Evaluation Criteria in Solid Tumours criteria v1.1 [32]. Overall survival (OS) was calculated using the Kaplan–Meier estimate.

## 3. Results

### 3.1. Patients and treatment

Forty-six patients were included for analysis; 37 (80%) were male, with a median age of 60 years (Table 1). A wide spectrum of cancers were included, the majority being melanoma (N = 33, 72%). Most patients (N = 41, 89%) had American Joint Committee on Cancer stage IV disease, and almost all patients (N = 43, 94%) had Eastern Cooperative Oncology Group performance status 0 or 1. Most patients (N = 35, 76%) received anti-PD-1/PD-L1 monotherapy, whereas seven and four patients (15% and 9%) received sequential and concurrent PD-1 and cytoxic T-lymphocyte antigen-4 (CTLA-4) therapy (ipilimumab), respectively. Six patients had a solid organ transplant, 12 patients had HIV, 14 patients had hepatitis B and 14 patients had hepatitis C.

The median OS of the cohort was 19.4 months (95% confidence interval, 13.2–25.6). Twelve patients (26%) had an objective response, and a total of 32 patients (70%) had disease control (complete/partial response or stable disease). irAEs occurred in 17 patients (37%), with five irAEs grade 3 or higher (11%).

### 3.2. Solid organ transplants

Six patients with a history of solid organ transplant were included, five with renal transplants and one with a liver transplant (Table 2). All had advanced melanoma; five were treated with anti-PD-1 monotherapy, and one was treated with sequential pembrolizumab and then ipilimumab. All patients were on immunosuppression at the start of immunotherapy.

Two patients (33%) developed graft rejection. One patient had acute rejection of a kidney transplant after one cycle of nivolumab, with subsequent graft failure despite IV methylprednisolone, and the sole liver transplant patient had acute rejection after one cycle of pembrolizumab, resulting in death after 18 days despite IV methylprednisolone, increased cyclosporine dosing and addition of tacrolimus and mycophenolate. A third patient had grade 2 pneumonitis, which responded to steroids. Two patients (33%) had partial responses, whereas the remainder had disease progression (N = 3) or death from toxicity (N = 1).

### 3.3. Patients with HIV

Twelve patients had concurrent HIV. Nine (75%) had melanoma, and three (25%) were co-infected with hepatitis B and/or C (Table 3). Seven patients (58%) were treated with anti-

PD-1/PD-L1 monotherapy, with five patients (42%) treated with sequential or concurrent PD-1 and CTLA-4 immunotherapy. Eleven patients (92%) were on anti-retroviral therapy (ART) at commencement (one unknown). Seven patients (58%) had viral loads recorded before commencement, with four undetectable (25%) and a median of CD4 count of 492 in the patients with evaluable counts. Seven (58%) had viral loads recorded during treatment.

Five patients (42%) developed conventional irAEs, with the only grade 3 event (colitis) occurring in a patient treated with concurrent ipilimumab and nivolumab. No HIV viral loads increased by one log or more during therapy, and there were two patients with HIV viral loads that decreased by one log or more during therapy; however, both were on ART. There were no events of immune reconstitution inflammatory syndrome. Four patients (33%) had a complete or partial response to therapy.

### 3.4. Patients with hepatitis B and C

Fourteen patients had hepatitis B; ten patients (71%) had melanoma and thirteen patients (93%) were treated with anti-PD-1/PD-L1 monotherapy (Table 4). Eight patients (57%) had viral loads measured at the start of treatment, four patients (29%) had an undetectable viral load at baseline and eight patients (57%) were on antiviral therapy. Five patients (36%) developed grade 1–2 conventional irAEs, with no higher grade events. No patients developed hepatitis, and no patients had a viral load increase of more than one log during therapy. Two patients had a viral load decrease of more than one log, with both patients being on concurrent anti-viral therapy. There were no viral load increases of one log or more. Three patients (21%) had a complete or partial response to therapy.

Fourteen patients had hepatitis C, nine (64%) had melanoma and ten (71%) were treated with anti-PD-1/PD-L1 monotherapy (Table 4). Eleven patients (79%) had viral loads measured at the start of treatment. Three patients (21%) had an undetectable viral load at baseline, and nine patients (64%) were on anti-viral therapy. Five patients (36%) had conventional irAEs, three (21%) of which were grade 3 or higher. Of note, one patient had grade 3 autoimmune hepatitis on concurrent ipilimumab and nivolumab; however, this patient's viral load was unavailable beyond the baseline measurement, and therefore the role of hepatitis C in this irAE is uncertain. Three patients (21%) had a viral load decrease of more than one log, with all three patients on concurrent anti-viral therapy. There were no viral load increases of one log or more. Three patients (21%) had a complete or partial response to therapy.

## 4. Discussion

The use of anti-PD-1/PD-L1 therapies for patients with cancer is rapidly increasing, but the safety and efficacy in populations with solid organ transplants or with chronic viral infections are largely unknown. In this series of patients with chronic viral infections—HIV or hepatitis B or C—we found that anti-PD-1/PD-L1 therapies can be safety used, with responses in up to a third of patients. The rates of both toxicity and efficacy appeared relatively similar to the rates observed in patients in clinical trials without such infections [33,34]. There were no increases in viral loads to suggest that anti-PD-1/PD-L1 therapy interferes with control of infection; on the contrary, a total of five patients with hepatitis B or

C and two patients with HIV had a decrease in viral loads while treated with anti-PD-1/PD-L1 therapy. Patients with solid organ transplantation, however, appear at a significant risk of early graft rejection and loss yet may also respond without toxicity.

Evidence from animal models with HIV and simian immunodeficiency virus (SIV) indicate that PD-1 blockade may contribute to improved viral load, antiviral immunity and survival [35,36], although a transient early increase in viral load before a reduction in viral load has been described in one SIV model [37] and a similar phenomenon has been reported in a single case report [38]. Similar to the HIV literature, there are supporting data from an animal model that PD-1/PD-L1 blockade can contribute to viral clearance of hepatitis B [39], and a small randomised trial of nivolumab in patients with hepatitis C but without malignancy showed promising reductions in viral load; however, only five of 42 patients treated with nivolumab met the primary end-point of a reduction in viral load of more than 0.5 log reduction [40]. However, two cases of reactivation of hepatitis B and one case of reactivation of hepatitis C have been reported [41–43]. In total, our data, coupled with similar experiences in the literature [29,30,44–46], support the use of anti-PD-1/PD-L1 therapy in patients with hepatitis B/C or HIV.

By contrast, previous case reports and data from this series suggest that there is a significant risk of graft rejection and death with anti-PD-1/PD-L1 therapy in patients with solid organ transplantation. Previous case reports have included 13 kidney [29,47–57], 14 liver [41,58–62] and two heart transplant recipients receiving anti-PD-1/PD-L1ebased immunotherapy [29], [63]. In total, eight of thirteen reported kidney transplant cases have resulted in rejection, one of two heart transplant cases resulted in rejection and four of fourteen liver transplant cases resulted in rejection. Adding these cases together with our series suggests a rate of rejection of nine out of eighteen (50%) in kidney transplant recipients and a rate of rejection of five out of fourteen (36%) in liver transplant recipients.

While responses occurred both in our cohort as well as in transplant recipients previously reported in the literature, the benefit of using anti-PD-1/PD-L1 therapy in this setting needs to be carefully weighed against the significant risk of transplant rejection and death. Although there is evidence suggesting that CTLA-4—based immunotherapy is associated with a lower risk of rejection and therefore perhaps could be considered in the first instance, the activity of CTLA-4 immunotherapy is low [29], [64]. In the circumstance where transplant rejection and graft failure are not acceptable outcomes, such as cardiac, lung or liver transplants, or renal transplant recipients who are not prepared to undergo dialysis, alternative regimens should be prioritised.

Our study had a number of limitations. There were limited longitudinal data on viral load during treatment for the HIV and hepatitis B and C cohorts, and similarly, there were limited data on anti-viral changes during treatment. Data on the degree of matching between transplant and recipient were unavailable, as well as immunosuppressant dosing and regimen changes during treatment. Given the retrospective observational design of this study, selection bias is also a potential limitation, however less so than in the case reports published so far. Further prospective studies are needed.

## 5. Conclusions

Patients with HIV or hepatitis B/C treated with anti-PD-1/PD-L1 therapy for malignancy can respond to immunotherapy with no apparent increase in toxicity compared with uninfected patients. In patients with solid organ transplants, graft rejection with graft failure and death can occur; alternatives should be sought where possible, and in the absence of alternatives, the potential benefits of anti-PD-1/PD-L1 therapy need to be carefully weighed against the mortality risk of untreated malignancy. These results provide not only important clinical information but also biological insight into the fundamental role and diverse function of the PD-1/PD-L1 pathway in cancer, infection and tolerance. Further research in these populations is warranted.

## Funding source

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**Table 1**

Baseline characteristics.

| Baseline characteristics | Number | Percentage |
|---|---|---|
| Median age | 60 | – |
| Male | 37 | 80% |
| ECOG performance status | | |
| 0 | 20 | 44% |
| 1 | 23 | 50% |
| 2 | 1 | 2% |
| Unknown | 2 | 4% |
| Cancer subtype | | |
| Melanoma | 33 | 72% |
| Urothelial carcinoma | 4 | 9% |
| Renal cell carcinoma | 2 | 4% |
| Mesothelioma | 2 | 4% |
| Hepatocellular carcinoma | 2 | 4% |
| Non-small cell lung cancer | 1 | 2% |
| Gastric cancer | 1 | 2% |
| Glioblastoma | 1 | 2% |
| AJCC stage | | |
| I | 1 | 2% |
| II | 1 | 2% |
| III | 3 | 7% |
| IV | 41 | 89% |
| Underlying condition | | |
| Solid organ transplant | 6 | 13% |
| HIV | 12 | 6% |
| Hepatitis B | 14 | 30% |
| Hepatitis C | 14 | 30% |
| Immunotherapy | | |
| Pembrolizumab | 21 | 46% |
| Nivolumab | 12 | 26% |
| Atezolizumab | 2 | 4% |
| Sequential PD-1 then CTLA-4 | 7 | 15% |
| Concurrent PD-1 and CTLA-4 | 4 | 9% |
| Total | 46 | |

ECOG: Eastern Cooperative Oncology Group; AJCC: American Joint Committee on Cancer.

**Table 2**

Solid organ transplant cohort.

| Organ | Cancer | Age | Gender | Immunotherapy | Immunosuppression | Toxicity | Response |
|---|---|---|---|---|---|---|---|
| Kidney | Melanoma | 65 | M | Sequential pembrolizumab + ipilimumab | Prednisone, mycophenolate and everolimus | G2 pneumonitis | PD |
| Kidney | Melanoma | 70 | M | Pembrolizumab | Tacrolimus and prednisone | – | PD |
| Kidney | Melanoma | 75 | M | Pembrolizumab | Prednisone | – | PR |
| Kidney | Melanoma | 65 | M | Pembrolizumab | Prednisone, mycophenolate and tacrolimus | – | PD |
| Kidney | Melanoma | 48 | M | Nivolumab | Prednisone and tacrolimus | G4 acute rejection of kidney transplant resulting in graft failure, requiring dialysis | PR |
| Liver | Melanoma | 63 | F | Pembrolizumab | Cyclosporine | G5 acute rejection of liver transplant. Death within 18 days of the first cycle | NE |

PR: partial response; PD: disease progression; irAE: immune-related adverse event; NE; not evaluable.

**Table 3**

HIV cohort.

| Cancer | Intercurrent infection | Immunotherapy | ART | CD4 count | Viral load | Response | IrAE |
|---|---|---|---|---|---|---|---|
| Melanoma | – | Concurrent ipilimumab + nivolumab | Rilpivirine, emtricitabine and tenofovir | 285-> 350-> 525 | <20 -> <20 | PR | – |
| Melanoma | Hep B | Concurrent ipilimumab + nivolumab | Raltegravir, emtricitabine and tenofovir | | | PR | G3 colitis |
| Melanoma | Hep C | Sequential pembrolizumab + ipilimumab | Emtricitabine, tenofovir and dolutegravir | 206- >269- >239- >347 | 160,624 -> <20 -> 30 | SD | G2 right facial palsy |
| Melanoma | – | Sequential pembrolizumab + ipilimumab | Efavirenz, emtricitabine and tenofovir | – | – | PD | – |
| Melanoma | – | Sequential nivolumab + ipilimumab | Nevirapine, abacavir and lamivudine | – | – | PD | – |
| Melanoma | – | Pembrolizumab | Unknown | – | <20 | SD | G2 nephritis |
| Melanoma | – | Pembrolizumab | Raltegravir, tenofovir and emtricitabine | 613-> 700 | <20-> <20 | CR | – |
| Melanoma | – | Pembrolizumab | Abacavir, darunavir and ritonavir | – | <40 -> <40 | PD | – |
| Melanoma | – | Pembrolizumab | Ritonavir, emtricitabine and tenofovir | – | – | SD | – |
| Urothelial carcinoma | – | Atezolizumab | Emtricitabine and tenofovir | 492 | – | PD | – |
| HCC | Hep B + C | Pembrolizumab | Emtricitabine, tenofovir and dolutegravir | 550- >550- >484 | 19,440-> <20 -> <20 | PR | G2 hypothyroidism |
| RCC | – | Nivolumab | Atazanavir, ritonavir, tenofovir and emtricitabine | | <20 | PD | G1 diarrhoea |

ART: anti-retroviral therapy; CR: complete response; PR: partial response; SD: stable disease; PD: disease progression; irAE: immune-related adverse event.

**Table 4**

Hepatitis B and C cohorts.

| Cancer | Viral hepatitis | Immunotherapy | Anti-viral therapy | Viral load (IU/ml) | Response | IrAE |
|---|---|---|---|---|---|---|
| Melanoma | Hepatitis B | Sequential pembrolizumab + ipilimumab | Nil | <20-> 20-> <20-> <20 | SD | – |
| Melanoma | Hepatitis B | Pembrolizumab | Tenofovir | <20-> 20-> <20-> <20 | SD | – |
| Melanoma | Hepatitis B | Pembrolizumab | Tenofovir | Unknown | PR | G2 hypothyroidism |
| Melanoma | Hepatitis B | Pembrolizumab | Entecavir | Unknown | PD | – |
| Melanoma | Hepatitis B | Pembrolizumab | Nil | Unknown | PD | – |
| Melanoma | Hepatitis B | Pembrolizumab | Nil | <20-> <20-> <20-> <20 | CR | G1 rash |
| Melanoma | Hepatitis B | Pembrolizumab | Nil | Unknown | PD | G2 rash |
| Melanoma | Hepatitis B | Nivolumab | Entecavir | 279-> 20-> <20-> 43 | SD | G2 pneumonitis |
| Melanoma | Hepatitis B | Nivolumab | Nil | 300-> 170 | PR | G1 vitiligo |
| Mesothelioma | Hepatitis B | Pembrolizumab | Entecavir | 467-> <20-> <20-> <20 | SD | – |
| Hepatocellular carcinoma | Hepatitis B | Nivolumab | Tenofovir | 39-> <20-> <20-> <20 | SD | – |
| Glioblastoma | Hepatitis B | Pembrolizumab | Entecavir | <20-> 20-> <20-> <20 | SD | – |
| Gastric carcinoma | Hepatitis B | Pembrolizumab | Nil | Unknown | SD | – |
| Urothelial carcinoma | Hepatitis B | Nivolumab | Entecavir | Unknown | SD | – |
| Melanoma | Hepatitis C | Concurrent nivolumab + ipilimumab | Sofosbuvir and ribavirin | 6,550,000-> undetectable | CR | G4 colitis |
| Melanoma | Hepatitis C | Concurrent nivolumab + ipilimumab | Ledipasvir and sofosbuvir | 9,360,000 | PR | G3 autoimmune hepatitis |
| Melanoma | Hepatitis C | Sequential nivolumab + ipilimumab | Ombitasvir, paritaprevir, ritonavir and dasabuvir | 1,218,319-> 920,912 | PD | – |
| Melanoma | Hepatitis C | Sequential pembrolizumab + ipilimumab | Interferon | 58,000 | CR | – |
| Melanoma | Hepatitis C | Pembrolizumab | Nil | Unknown | SD | G3 adrenal insufficiency |
| Melanoma | Hepatitis C | Pembrolizumab | Nil | Unknown | SD | – |
| Melanoma | Hepatitis C | Pembrolizumab | Ribavirin and pegylated interferon | Undetectable | PD | – |
| Melanoma | Hepatitis C | Nivolumab | Nil | Undetectable | SD | – |
| Melanoma | Hepatitis C | Nivolumab | Nil | Unknown | SD | – |

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| Cancer | Viral hepatitis | Immunotherapy | Anti-viral therapy | Viral load (IU/ml) | Response | IrAE |
|---|---|---|---|---|---|---|
| Urothelial carcinoma | Hepatitis C | Nivolumab | Ribavirin and pegylated interferon | 81,159 | SD | G1 rash |
| Urothelial carcinoma | Hepatitis C | Atezolizumab | Ledipasvir and sofosbuvir | Undetectable | SD | – |
| Mesothelioma | Hepatitis C | Pembrolizumab | Unknown | 903,029 | SD | – |
| Renal cell carcinoma | Hepatitis C | Nivolumab | Ledipasvir and sofosbuvir | 379,836-> Undetectable | SD | – |
| Non-small cell lung cancer | Hepatitis C | Nivolumab | Ledipasvir and sofosbuvir | 3,952,419-> undetectable | SD | – |

CR: complete response; PR: partial response; SD: stable disease; PD: disease progression; irAE: immune-related adverse event.