Case Report

Resumption of anti-programmed cell death 1 monotherapy for severe immune-related adverse events experienced patient with renal cell carcinoma

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Abbreviations & Acronyms
CT = computed tomography
CTLA-4 = cytotoxic-T-lymphocyte antigen 4
ICI = immune checkpoint inhibitor
Ipi = ipilimumab
irAE = immune-related adverse event
Nivo = nivolumab
PD-1 = programmed cell death 1
PSL = prednisolone
RCC = renal cell carcinoma

Introduction: Combined anti-cytotoxic-T-lymphocyte antigen 4 and programmed cell death 1 blockade induced high rates of immune-related adverse events in patients with renal cell carcinoma. However, the safety of reinitiating anti-programmed cell death 1 monotherapy for patients who discontinued combination therapy due to immune-related adverse events is largely unknown.

Case presentation: We report the case of a 74-year-old man who received combination therapy with anti-cytotoxic-T-lymphocyte antigen 4 and programmed cell death 1 inhibitors for advanced renal cell carcinoma. After three cycles of combination therapy, he complained severe immune-related adverse events including grade 3 nausea and anorexia, and grade 3 diarrhea, leading to discontinuation of the therapy. He started readministration of anti-programmed cell death 1 monotherapy at 41 weeks after discontinuation due to the new lung metastatic lesion. Importantly, he experienced only grade 1 diarrhea, which can be controlled with prednisolone.

Conclusion: The readministration of anti-programmed cell death 1 monotherapy with close monitoring can be an acceptable treatment even after discontinuation of combination therapy.

Key words: immune checkpoint inhibitor, immune-related adverse event.

Keynote message

The safety of resuming anti-PD-1 monotherapy for patients who discontinued ICIs due to irAEs is still unknown. We report an instructive case with advanced RCC who carefully resumed anti-PD-1 inhibitor after discontinuation of dual CTLA-4 and PD-1 blockade due to severe irAEs.

Introduction

ICIs have revolutionized the field of cancer in recent years and remarkably improved the prognosis of several types of cancer.¹ As ICIs have been used over the years, a certain number of patients face discontinuation of ICIs due to severe and sometime life-threatening irAEs.² Especially, combination of CTLA-4 and PD-1 inhibitors, ipilimumab and nivolumab, was shown to increase the incidence of irAEs compared to that of either monotherapy despite of the high response rate.³,⁴

Normally, patients with high-grade irAEs require discontinuation of both ipilimumab and nivolumab with the administration of corticosteroids. After treatment-free duration, physicians often need to choose secondary treatment in the face of progressive disease. Considering that most severe toxicities occur within 3 months after initiation of combination therapy, readministration of anti-PD-1 monotherapy can be the optional treatment to achieve durable disease control. However, the safety and efficacy of resuming anti-PD-1 monotherapy is still largely unknown.

Here, we report an instructive case with advanced RCC who carefully resumed anti-PD-1 inhibitor after discontinuation of dual CTLA-4 and PD-1 blockade due to severe irAEs.
Case presentation

A 74-year-old man with no significant medical history presented with his left clavicular pain. A chest X-ray showed a neoplastic fracture in the left clavicle. Abdominal and chest CT examination revealed the renal mass with early enhancement in right kidney with 35 mm diameter (Fig. 1). In addition, CT scan showed osteolytic mass in the left clavicle, left iliac crest, and small nodule in middle lobe of the right lung (Fig. 1). It is the basic policy of our institution to recommend radical nephrectomy for clinical stage T1 and T2, and subsequently he underwent laparoscopic radical nephrectomy. The pathological examination showed clear cell RCC (Fuhrman grade 2) with tumor invasion of perirenal fat, leading to the diagnosis of stage pT3aN0M1. With a diagnosis of left clavicle and iliac bone metastasis, the patient received the treatment with zoledronic acid 4 mg intravenously every 4 weeks.

According to the International Metastatic RCC Database Consortium score, the patient was classified as poor risk (<1 year from time of diagnosis to systemic therapy, Karnofsky Performance Status 70, low hemoglobin value) and began to receive nivolumab plus ipilimumab combination therapy for his multiple metastatic sites.

After one cycle of combination therapy, he felt listlessness of the right forearm and difficulty in speaking clearly. The brain magnetic resonance imaging showed a brain metastasis and cyber knife therapy was performed for brain metastasis (Fig. 2). In parallel with radiotherapy, the patient received the second course of the combination therapy. Two weeks later, he complained of grade 3 nausea and anorexia. He also experienced grade 3 diarrhea, grade 2 liver dysfunction, and grade 1 rash, leading to discontinuation of third course of combination therapy (Fig. 2). We suspected severe irAEs due to various symptoms, but we were unable to exclude the possibility of bacterial enteritis and started the administration of 40 mg (1 mg/kg per day) PSL for the patient. With the negative test result of fecal culture, the dose of PSL was increased to 80 mg and irAEs gradually improved within next 7 weeks. Finally, the dose of PSL was tapered to 7.5 mg. Metastatic sites maintained partial response for 30 weeks after the discontinuation of ICIs without any additional therapy (Fig. 3a). However, follow-up CT examination showed the new lung metastatic lesion after 41 weeks after discontinuation (Fig. 3b) and we decided to start readministration of nivolumab monotherapy (Fig. 4). As a result, he experienced only grade 1 diarrhea after three cycles of nivolumab, which can be controlled with the temporary increasing dose of PSL. Importantly, any other irAEs such as nausea, anorexia, liver dysfunction, and rash did not appear after the introduction of nivolumab monotherapy.

Follow-up CT scan at 12 weeks after the introduction of nivolumab showed the increase in lung and iliac bone metastasis, leading to withdrawal of nivolumab and subsequent axitinib therapy.

Discussion

Immunotherapy targeting immune checkpoint is now the most attractive therapy in cancer field. Particularly, combination
of ICIs expands the application to various types of cancer as
the first-line therapy because of the high response rate. At
the same time, it is undeniable that a certain population of
patients are forced to discontinue combination therapy
because of severe irAEs. However, there is no conclusive evi-
dence that determine which second-line therapy is suitable in
patients with progressive disease after disconnection of
ICIs.

Fig. 2 Clinical course of the case with severe
irAEs induced by ipilimumab and nivolumab. After
two cycles of combination therapy, the patient
showed severe irAEs such as grade 3 nausea and
anorexia, and grade 3 diarrhea. All symptoms
gradually resolved within next 7 weeks after
discontinuation of combination therapy and
additional treatment of PSL.

Fig. 3 Sequential CT scans after discontinuation
of combination therapy. (a) Abdominal CT scans
show that the metastatic site of iliac bone
maintained partial response for 30 weeks after
the discontinuation of combination therapy
without any additional therapy. After 41 weeks
after discontinuation follow-up, CT showed
reduction of iliac bone metastatic sites. (b) Chest
CT scan shows the new lung metastatic lesion at
41 weeks after discontinuation and the patient
was diagnosed as progressive disease. The
number of weeks indicates duration after the first
initiation of combination therapy.

Fig. 4 Clinical course after the readministration
of nivolumab for progressive disease. The patient
experienced only grade 1 diarrhea after
readministration of nivolumab. The symptom
promptly resolved with temporary increasing
dose of PSL.
In this study, we report a patient who experienced severe irAEs while on combination therapy of ipilimumab and nivolumab, and were cautiously reinitiated with anti-PD-1 monotherapy after certain duration of discontinuation. Interestingly, at the reinitiation phase with nivolumab, the patient experienced only grade 1 diarrhea. Pollack et al. reported almost 40% of 80 melanoma patients who discontinued combination therapy experienced recurrent or clinically significant distinct (de novo) irAEs with anti-PD-1 monotherapy reinitiation.\(^6\) They concluded that most of recurrent or distinct irAEs were low-grade and manageable with corticosteroid treatment, while they had one case of grade 5 Stevens–Johnson syndrome. In other study, the same or different irAEs occurred in 55% of patients with resuming anti-PD-1 or anti-PD-L1 therapy and were not found to be more severe than the first.\(^7\) Given that major irAEs (e.g. colitis, hypophysitis) of combination therapy are largely associated with ipilimumab at the first line of treatment, anti-PD-1 resumption with careful monitoring of irAEs may be one of the options to achieve further clinical response, although further cases are needed to judge the efficacy of anti-PD-1 resumption.

In conclusion, with intent to “cure” for cancer, the readministration of anti-PD-1 monotherapy may be considered as a durable and feasible option for RCC patients who discontinued combination therapy.

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Conflict of interest

The authors declare no conflict of interest.

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Editorial Comment

Editorial Comment to Resumption of anti-programmed cell death 1 monotherapy for severe immune-related adverse events experienced patient with renal cell carcinoma

In this issue, Maegawa et al.\(^1\) reported on the safety and efficacy of reinitiating nivolumab monotherapy in a case who discontinued combination therapy of nivolumab and ipilimumab due to immune-related adverse events (irAEs). Although the development of immune-checkpoint inhibitors (ICIs) has changed the treatment of advanced renal cell carcinoma, the clinical practitioners are confronted with a problem of whether ICIs should be reinitiated following recovery from severe irAEs.

So far, several case-series studies on the incidence of irAEs with the resumption of ICIs after a discontinuation due to irAEs were reported. Santini et al. reported that 26% had recurrence of the initial irAEs, and 26% had new irAEs in advanced non-small cell lung cancer.\(^2\) In the study by Pollack et al., 18% had recurrent irAEs, and 21% had distinct toxicities in metastatic melanoma.\(^3\) Simonaggio et al. showed that 42.5% and 12.5% had recurrence of the same and different irAEs in various cancers, respectively.\(^4\) Notably, two (pneumonitis, colitis) and one (Stevens–Johnson syndrome) treatment-related deaths occurred after the resumption of anti-PD-(L)1.\(^2,3\) Accordingly, great caution is required when ICIs are re-administered after irAEs. Remaining on steroid therapy at resumption, and shorter time to initial irAEs were suggested to be associated with recurrent irAEs in resumption, which might be useful to estimate the risk of irAEs re-emergence.\(^3,4\)

With regard to the efficacy of ICIs resumption, Santini et al. demonstrated favorable prognosis with the resumption of anti-PD-(L)1 although statistical power is not enough. In the study by Pollack et al., 31% had partial responses, 23% had stable disease, and 46% had progressive disease among patients underwent resumption of ICIs for disease progression after discontinuation.\(^3\) Simonaggio et al., 32.5% had a partial response, 37.5% had stable disease, and 22.5% had progressive disease during the resumption of ICIs.\(^4\) Collectively, data on the efficacy of resumption suggest a promise of ICI re-challenge in selected patients.

Thus, re-challenge of ICIs shows expected tumor response in exchange for higher risk of irAEs, which can rarely be lethal. In line with these previous reports, this case report demonstrated controllable irAE after resumption of nivolumab although objective response was not obtained. Since there is no established evidence supporting the usefulness of

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