

Treatment with pembrolizumab after hypersensitivity reaction to nivolumab in a patient with hepatocellular carcinoma

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Purpose. The options for immunotherapy treatment are limited for treatment of hepatocellular carcinoma. In this case study, we report a case of successful alternation of one PD-1 inhibitor for another after a hypersensitivity reaction.

Summary. Nivolumab (Opdivo, Bristol-Myers Squibb) has been Food and Drug Administration (FDA) approved for a variety of malignancies, including a recent approval for hepatocellular carcinoma (HCC). Infusion-related reactions occur in less than 1% of patients, and although such reactions are rare, recognition of infusion-related reactions induced by nivolumab is an important aspect of its usage. The PD-1 checkpoint inhibitor pembrolizumab is also FDA approved for subsequent-line therapy in treatment of HCC. Thus far, approximately 0.2% of patients experienced severe infusion-related reaction in studies using pembrolizumab. A 70-year-old male with HCC had an infusion reaction to nivolumab that presented as facial flushing, dyspnea, and back pain. The patient received prompt administration of diphenhydramine and hydrocortisone, which led to the amelioration of symptoms and allowed the patient to complete his immunotherapy treatment. For the third dose of nivolumab, the patient received premedications prior to treatment, including diphenhydramine, hydrocortisone, and famotidine. During his infusion, the patient experienced facial flushing, coughing, chest tightness, and an itchy throat. The patient again received diphenhydramine and hydrocortisone to treat infusion-related symptoms and his therapy was discontinued. Because of the nivolumab infusion-related reaction, nivolumab was discontinued, and the patient was started on pembrolizumab. The patient tolerated pembrolizumab without any subsequent infusion-related reactions. Prompt recognition and attention to immunotherapy infusion-related reactions could potentially prevent the fatal complication of anaphylaxis with immune checkpoint inhibitors. In this report, we describe the successful transition from one anti-PD-1 therapy to another for continued immunotherapy treatment without any subsequent infusion reactions.

Conclusion. A patient with HCC was successfully treated with pembrolizumab after experiencing adverse effects with nivolumab.

Keywords: carcinoma, hypersensitivity, infusion-related reaction, nivolumab, pembrolizumab, renal cell

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Tumor cells express programmed cell death ligands 1 and 2, which interact with programmed cell death protein 1 (PD-1) receptors, which prevent cytotoxic T cells from destroying tumor cells. Nivolumab, a fully human immunoglobulin G4 (IgG4) monoclonal

antibody, is an immune checkpoint inhibitor approved by the Food and Drug Administration (FDA) for various cancers, including advanced melanoma, renal cell carcinoma, Hodgkin disease, non-small cell lung cancer, small cell lung cancer, colorectal cancer, and

hepatocellular carcinomas (HCC).¹ Nivolumab restores the cytotoxic T cell's ability to destroy tumor cells by blocking the PD-1 receptor.^{2,3} Based on improved objective response rates, nivolumab has provided the option of a second-line therapy in HCC.⁴ Nivolumab may cause severe infusion-related reactions in less than 1% of cases. For the single agent therapy of nivolumab, 2.2% and 2.7% of treated cases experienced infusion-related reactions within 30 minutes and 60 minutes, respectively. These cases presented with flushing, chills or shaking, itching or rash, fever, dizziness, dyspnea, and fainting.⁵

Nivolumab-induced infusion-related reactions demonstrate the necessity of early recognition, successful management, and alternative therapy options. Another IgG4 monoclonal antibody, pembrolizumab, is an immune checkpoint inhibitor that works similarly to nivolumab. Pembrolizumab is also FDA approved for subsequent-line therapy in treatment of HCC.⁶ Pembrolizumab binds to the PD-1 receptor reversing the cytotoxic T cell's tumor-killing ability. With a similar mechanism of action, the adverse effect profile of pembrolizumab is similar to those of nivolumab.² Infusion-related reactions occur in 0.2% of the cases.⁶ Pembrolizumab is now approved as a second-line therapy for HCC.⁷ Because of its poor prognosis and limited number of therapies, an alternative therapy in case of toxicity from an FDA-approved therapy is necessary and should be explored.

Case presentation

A 70-year-old male with a past medical history of gastroesophageal reflux disease, gastritis, and renal cell carcinoma status post right radical nephrectomy in 2016 was diagnosed with hepatocellular carcinoma of a stage at which primary, regional lymph nodes, and distant metastasis cannot be measured. The purpose of his therapy was palliative care. The patient previously received radioembolization treatments on January 22, 2018, and sorafenib on February 20, 2018. The patient had no allergic history prior to his infusion-related

KEY POINTS

- The options for therapy are often limited in an oncology setting.
- Infusion-related reactions, although rare, can occur with use of a programmed cell death protein 1 (PD-1) inhibitor for cancer treatment.
- In this case report, the switch from one PD-1 inhibitor to another was tolerated without risk of an infusion-related event during treatment.

reaction to nivolumab. The patient verified taking the following oral medications through a review conducted on October 11, 2018: benzonatate 100 mg 3 times daily as needed, lisinopril 5 mg daily, sertraline 25 mg daily, docusate daily, ferrous sulfate, multivitamin daily, guaifenesin with dextromethorphan every 6 hours as needed, and fish oil 200 mg daily. Although the patient was required to provide the medication list at every visit, a pharmacist reconciled the medication list on October 11, 2018, therefore the list from this date was included. Home medications were continued during the patient's stay.

The patient was started on nivolumab therapy to slow down the progression because computed tomography imaging on July 2, 2018, showed a new small area of presumed subpleural scarring of the left upper lobe with several new punctate nodules in the lungs. The first nivolumab 240 mg infusion was given on July 17, 2018. Per the institution's protocol, famotidine 20 mg i.v., diphenhydramine 25 mg i.v., and hydrocortisone 100 mg i.v. were given before the infusion. The infusion is given via smart pump, which has a set infusion rate entered in the machine. The patient tolerated the first dose without any complications. He presented to the infusion clinic for the second infusion of nivolumab

on July 31, 2018. Ten minutes into the nivolumab infusion, the patient reported facial flushing and shortness of breath with lower back pain. He did not experience any fever or hypotension. The treatment medication was stopped, and the patient was administered oral diphenhydramine 25 mg and hydrocortisone 100 mg i.v. The nivolumab infusion was then restarted approximately 30 minutes after the resolution of symptoms at half the previous infusion rate. The patient tolerated the remaining nivolumab infusion without any symptoms and issues. He was discharged with another infusion appointment scheduled in 2 weeks.

The patient returned to the infusion clinic for the third dose of nivolumab 240 mg i.v. At this visit, the patient was clinically assessed before the infusion. He denied having shortness of breath and fever. The patient's lungs were clear to auscultation and percussion and nonlabored respiration was reported. On arrival, the patient received a pre-medication treatment of diphenhydramine 25 mg i.v., famotidine 20 mg i.v., and hydrocortisone 100 mg i.v. Eleven minutes into the infusion, the patient developed facial flushing, chest tightness, and cough and described having an itchy throat. Initially, the patient was given diphenhydramine 25 mg and then an additional hydrocortisone 50 mg. The infusion was stopped, and per assessment, the patient still reported having chest tightness for 20–30 minutes after the infusion.

Vitals were reported to be stable with a heart rate of 84 bpm, temporal temperature of 36.7°C, respiration rate of 16 breaths per minute, an oxygen saturation of 96%, with the exception of blood pressure of 134/91. The facial flushing and cough were resolved. Because of repeated infusion-related reactions, a team decided that the patient would not be rechallenged with nivolumab at this visit. The patient was observed in the infusion center for 45 minutes and then discharged from the infusion clinic. Because of the worsening infusion reactions, nivolumab was discontinued and the patient was switched to pembrolizumab.

The patient visited the infusion clinic 2 weeks later for the first infusion of pembrolizumab supported by the recent publication of off-label pembrolizumab use in sorafenib-treated hepatocellular carcinoma as a second-line therapy.⁷ Methylprednisolone 125 mg i.v. and acetaminophen 650 mg by mouth were given to the patient as premedication 30 minutes prior to the infusion. Pembrolizumab 200 mg i.v. was infused over 30 minutes, and the patient tolerated the infusion without any complications. He received a second dose of pembrolizumab on September 18, 2018, without any subsequent infusion-related reactions. Unfortunately, a magnetic resonance imaging study from September 14, 2018, showed progression of disease, and the patient presented with an intractable cough on October 9, 2018. Therefore, pembrolizumab was discontinued on October 9, 2018, and the patient started cabozantinib. The patient received three doses of nivolumab and two doses of pembrolizumab total.

Discussion

The reported infusion-related reactions are a definite adverse drug reaction according to the Naranjo nomogram assessment form.⁸ The Naranjo nomogram was used to ensure that the adverse reaction the patient experienced was actually due to the drug and not from other factors. An infusion-related reaction is defined as a disorder characterized by an adverse reaction to the infusion of pharmacological or biological substances. Per the National Cancer Institute's Common Terminology Criteria for Adverse Events, these adverse events are defined as infusion-related reactions, the first event being grade 2 and the second reaction being grade 3.⁹ For nivolumab, the cases of infusion reactions is less than 1%. When nivolumab was given as a single agent over 30 minutes or 60 minutes, infusion-related reactions occurred in 2.2% (8 of 368) and 2.7% (10 of 369), respectively. Additionally, 0.5% (2 of 368) and 1.4% (5 of 369) of patients, respectively, experienced

adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation, or the withholding of nivolumab.⁴ The National Comprehensive Cancer Network guideline on management of immune checkpoint inhibitor-related toxicities recommends the discontinuation of the immunotherapy permanently for severe infusion-related reactions such as those this patient experienced.¹⁰ There has been a case report of a patient with stage IV lung squamous cell carcinoma who had an infusion-related reaction to a second dose of nivolumab within 15 minutes into the infusion.¹¹ Supportive measures included nasal oxygen inhalation, chlorpheniramine, and methylprednisolone for prophylaxis as compared with our patient who received diphenhydramine and hydrocortisone. However, this published case report states that the patient was able to receive the second dose of nivolumab on a different day. Because our patient had another infusion-related reaction on the day of the third dosing, nivolumab was stopped and the patient required an alternative therapy to continue his immunotherapy. Secondary to the repeat infusion reactions with nivolumab, pembrolizumab was given to this patient because the effectiveness of pembrolizumab is supported in a phase II study.³ Although pembrolizumab has the same mechanism of action as nivolumab, the patient did not experience an infusion-related reaction to this drug. To our knowledge, this case report is the first to show that substituting pembrolizumab for nivolumab secondary to infusion-related reactions may provide a safe option for continued treatment with immunotherapy.

Conclusion

A patient with HCC was successfully treated with pembrolizumab after experiencing adverse effects with nivolumab.

Disclosures

The authors have declared no potential conflicts of interest.

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