Dramatic Response of a Metastatic Primary Small-Cell Carcinoma of the Pancreas to a Trial of Immunotherapy with Nivolumab: A Case Report

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Abstract

Extrapulmonary small-cell neuroendocrine cancers are rare in clinical practice. They are frequently metastatic at the time of diagnosis with survival in months even with the most intensive treatment. So far, treatment recommendations for this group rely on data from the similar but more common small-cell carcinoma of the lungs. Immune checkpoint inhibitors are being investigated for the treatment of metastatic small-cell lung cancer with positive outcome. We applied the experience from these studies to a case of metastatic small-cell neuroendocrine cancer of the pancreas using nivolumab as a treatment of last resort. We noted a favorable and durable response suggesting that this may be superior to all currently available options for palliative treatment in a similar scenario.
Background

Primary small-cell carcinoma of the pancreas (SCCP) is a rare neuroendocrine carcinoma accounting for less than 2% of cancers of pancreatic origin. It carries a poor prognosis similar to small-cell lung cancer (SCLC) with limited treatment options for metastatic disease. Recent clinical trials have demonstrated favorable response of SCLC to treatment with the immune checkpoint inhibitor (ICI) nivolumab. Nivolumab was initially approved by the Food and Drug Administration (FDA) in 2014 for the treatment of metastatic melanoma. It has rapidly gained approval for the treatment of advanced stages of five other malignancies, namely non-SCLC, renal cell carcinoma, squamous cell carcinoma of the head and neck, classic Hodgkin’s lymphoma, and urothelial carcinoma. Nivolumab is not approved by the FDA for the treatment of small-cell carcinoma; in fact, there are no approved targeted therapies or non-chemotherapy options in patients with small-cell carcinoma. Here, we report a dramatic response of a patient with SCCP who experienced progression on approved first- and second-line treatment to a trial immunotherapy with nivolumab.

Case Description

Our patient is a 59-year-old female with a significant past medical history of hypertension, iron deficiency anemia, and tobacco dependence amounting to a 40-pack-year smoking history. She initially presented to her primary care physician (PCP) with a 6-month history of generalized fatigue with associated symptoms of anorexia and a 20-pound unintended weight loss. Fearing the possibility of a lung cancer, her PCP obtained a computed tomography (CT) scan of the chest, which showed a 3-mm nodule in the right lower lobe of the lungs, multiple heterogeneous hepatic lesions, the largest of which measured 7.2 × 5.6 cm, and a hypoattenuating lesion measuring 4.8 × 3.1 cm at the tail of the pancreas (Fig. 1). A follow-up CT scan of the abdomen and pelvis re-demonstrated these findings with multiple enlarged periaortic lymph nodes. At the same time, her laboratory test revealed elevated liver transaminases and cancer antigen 19-9 level. An ultrasound-guided core biopsy of the liver was performed and histology confirmed liver lesions to be small-cell carcinoma, poorly differentiated. Positron emission tomography (PET) scan showed uptake consistent with malignancy in the liver and pancreas, but no PET-avid lesions were seen anywhere else.

After discussing the diagnosis and treatment options with the patient, she elected to proceed with palliative chemotherapy. She was started on a standard regimen of carboplatin and etoposide. Restaging scans after two cycles showed great response with some reduction in the sizes of both the hepatic and pancreatic lesions. The subsequent imaging after 6 cycles showed a stable disease. She was at this time referred to a tertiary teaching hospital where she was evaluated for a clinical trial but was found ineligible to participate. Unfortunately, repeat CT scan of the abdomen and pelvis 2 months after completing 6 cycles of palliative chemotherapy showed disease progression with increase in the sizes of the previously seen hepatic lesion and new metastatic lesions. She was subsequently started on topotecan. A restaging scan performed after cycle 2 of second-line palliative chemotherapy showed further disease progression (Fig. 2). She had a good ECOG performance status of 1. We reviewed the treatment goals and options with the patient once again. We introduced the idea of a trial of nivolumab based on preliminary results of CheckMate 32 studies showing favorable outcomes for the treatment of recurrent SCLC and she welcomed the idea. A repeat CT scan after 5 weeks and 4 doses of nivolumab treatment showed a reduction in size of the
largest hepatic lesion from 7.2 x 6.6 cm to 4.8 x 3.7 cm and the number of hepatic metastases. Similarly, the pancreatic tail mass was decreased in size from 3.7 x 3.5 cm to 3.6 x 2.4 cm (Fig. 3).

Discussion

Primary SCCP is rare. Fewer than 50 cases have been reported in the literature; hence, there is limited knowledge about its natural history, treatment options, and outcomes. Clinically, they appear to behave in ways that resemble histologically similar SCLC including their tendency to be widely metastatic at the time of diagnosis with poor prognosis [1, 2], better initial response to chemotherapy [3], and their association with paraneoplastic syndrome [4–6]. Two reviews of previously reported cases suggest average age at diagnosis in the sixth decade of life, widely varying survival, and male preponderance of cases with most tumors originating in the head of the pancreas [1, 2]. In most reports, untreated patients died within 2 months of diagnosis [1, 7]. Because of lack of evidence-based treatment, most cases with advanced disease have been treated similar to SCLC with platinum-based chemotherapy [3]. Aggressive surgical treatment was reported in several case reports. Winter et al. [8] reported a review of six of such cases treated at the Johns Hopkins Hospital and Mayo Clinic, some of whom were treated with surgery and adjuvant chemoradiotherapy. They compared these cases to seven cases in different case reports treated with surgery or surgery and chemotherapy. Their findings suggest that the addition of the trimodality treatment with surgery, chemotherapy, and radiotherapy in their series likely resulted in a doubling of survival with a record median survival of 20 months. Of note, the majority of these patients had early-stage and locally advanced disease only.

Our patient with stage IV SCCP with multiple metastatic liver lesions was initially treated with cisplatin and etoposide followed by topotecan. She continued to progress on this second-line agent. Unlike non-SCLC, there are no approved targeted or immunotherapy options for SCLC and related extrapulmonary small-cell neuroendocrine cancers. Emerging data suggest that ICIs may have meaningful clinical activity in SCLC. The initial result of the CheckMate 32 trial showed that patients with advanced-stage SCLC who progressed after one or more platinum-based chemotherapy experienced durable objective response with either single-agent immunotherapy with nivolumab or combination of nivolumab and ipilimumab [9]. Similarly, initial analysis of patients in the Keynote-28 trial with advanced programmed death-ligand 1 (PD-L1)-positive SCLC who failed standard treatment has shown a durable response in 31% of patients to treatment with pembrolizumab [10]. A case report has previously reported an excellent result for a trial of nivolumab on a patient with recurrent metastatic PD-L1-negative small-cell neuroendocrine carcinoma of the cervix, another rare type of extrapulmonary small-cell cancer [11]. In that case, treatment was limited due to side effects. With our patient, nivolumab resulted in rapid and durable objective response. Moreover, other than autoimmune thyroiditis and mild colitis, the patient tolerated the treatment well. To the best of our knowledge, this is the first report showing immunotherapy benefits in patients with SCCP.

Although SCLC is not yet an approved indication for ICIs, a search on trials.gov indicates that studies are moving ahead to explore the numerous ways ICIs can be used in the treatment of SCLC including their simultaneous combination with other treatment modalities. The CheckMate 451 trial is exploring the role of nivolumab in combination with ipilimumab or placebo as a Consolidative treatment in patients with extensive-stage SCLC who remain
stable or are responding to an initial completed cycle of platinum-based chemotherapy. In this same population, one ongoing study and one completed study have been designed to evaluate the outcome of combining ICIs with chemotherapy, specifically pembrolizumab plus cisplatin plus etoposide and ipilimumab plus carboplatin plus etoposide, respectively, with a focus on outcomes such as tolerability and progression-free survival. Similarly, another ongoing study evaluates the effects of ipalimumab plus nivolumab plus thoracic radiotherapy after 4–6 cycles of platinum-based chemotherapy on 6-month progression-free survival. Information derived from these studies will likely place ICIs in the center stage of advanced SCLC treatment and without doubt advance the treatment of closely related extrapulmonary small-cell neuroendocrine tumors such as SCCP.

Conclusion

Similar to SCLC, cisplatin-based chemotherapy has been the mainstay of treatment for most histologically similar extrapulmonary small-cell cancers. However, there are very limited treatment options once the patients become either platinum refractory or cannot tolerate platinum agents. We successfully used immunotherapy in our patient with SCCP, which resulted in a remarkable response as evidenced by a reduction in number and size of her metastatic liver lesions and appears to have durable response. This report suggests that ICIs may be active in SCCP, with potential for dramatic responses in a subset of patients.

Statement of Ethics

Written informed consent was obtained from the patient.

Disclosure Statement

The authors did not receive any form of funding or sponsorship for this publication and have no conflict of interest to declare.

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Fig. 1. CT of the abdomen and pelvis showing pancreatic and liver masses at the time of diagnosis.
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Fig. 2. CT of the abdomen and pelvis after 2 months on second-line chemotherapy showing a lack of reduction in size of the liver lesion.

Fig. 3. CT scan showing a marked reduction in size of the liver lesion after 5 weeks of nivolumab.