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Brief Communication

BRIEF COMMUNICATION

Thinking Critically About Classifying Adverse Events: Incidence of Pancreatitis in Patients Treated With Nivolumab + Ipilimumab

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Abstract

The Common Terminology Criteria for Adverse Events (CTCAE) were developed to document the adverse effects of chemotherapy but are now also used to document immune-related adverse events (irAE). Characterization of irAE by the CTCAE has implications for determining dose-limiting toxicity (DLT) and, consequently, the recommended phase II dose (RP2D) of investigational agents. In the phase I trial of nivolumab + ipilimumab, an asymptomatic increase in lipase was the primary DLT that informed the RP2D. We performed a retrospective study of 119 patients with melanoma who were treated at Memorial Sloan Kettering Cancer Center with the combination of nivolumab + ipilimumab to investigate the relationship between asymptomatic grade 3 or higher increases in amylase and/or lipase and pancreatitis, a known irAE. Of the 119 patients, there were only two cases of pancreatitis, representing 20% of patients with grade 3 or higher amylase, 6.3% of patients with grade 3 or higher lipase, and 20% of patients with grade 3 or higher elevations of both enzymes. The application of the CTCAE, especially in grading independent lab values, should be considered carefully in clinical trials of novel immunotherapeutic agents.

In cancer clinical trials, adverse events (AEs) are reported using the United States National Cancer Institute's (NCI's) Common Terminology Criteria for Adverse Events (CTCAE) (1). The original CTCAE were developed to document the adverse effects of chemotherapy (1) but are also used to in immuno-oncology trials to document side effects termed "immune-related adverse events" (irAE). The NCI is aware of the need to continually reevaluate the CTCAE to ensure they accurately capture clinical events. This is critical as characterization of AEs by the CTCAE has implications for determining what constitutes a dose-limiting toxicity (DLT) and, consequently, the recommended phase II dose (RP2D) of investigational agents.

One example of this is the phase I trial (CA209004) of nivolumab + ipilimumab in which cohorts of patients with advanced melanoma were treated with escalating doses (2). The most common grade 3–4 treatment-related irAE was an elevation in lipase, seen in 13% of patients (2). The dose cohort of ipilimumab 3 mg/kg + nivolumab 3 mg/kg was determined to have exceeded the acceptable levels of DLTs because of three patients having asymptomatic grade 3 or higher lipase elevations lasting for

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three or more weeks. It remains unclear whether additional dose escalation would have increased the efficacy of this immunotherapy approach as less frequent and lower doses of ipilimumab have also led to impressive efficacy (3,4). Nonetheless, these elevated laboratory values in the phase I study contributed to the determination of the 3 mg/kg of ipilimumab + 1 mg/kg of nivolumab dosing for subsequent studies in melanoma, ultimately leading to US Food and Drug Administration (FDA) approval (2,5,6).

Given this history, we were interested in the correlation between elevations in amylase and lipase with pancreatitis, a known irAE (7). According to the Classification of Acute Pancreatitis, pancreatitis is a clinical diagnosis in which two of the three components are present: elevation in amylase or lipase to 3X the upper limit of normal (ULN), characteristic symptoms of severe epigastric pain, or radiographic findings (8).

We performed a retrospective review of 119 patients at Memorial Sloan Kettering Cancer Center (MSKCC) with melanoma treated with the combination of nivolumab + ipilimumab on protocols CA209004 (n = 39) (2), CA209069 (n = 16) (6), and CA209218 (n = 64) to characterize the relationship between asymptomatic grade 3 or higher increases in amylase and/or lipase and their association with pancreatitis. Amylase and lipase levels were graded per protocol according to CTCAE v. 3.0 or v. 4.0 (1). We reviewed the patients with elevated amylase and/or lipase values grade 3 or higher for a subsequent diagnosis of pancreatitis.

All of the patients treated on CA209069 and CA209218 received doses of ipilimumab 3 mg/kg and nivolumab 1 mg/kg; in protocol CA209004, 10 patients received that dose level. Of the 119 patients, 10 (8.4%) had grade 3 or higher amylase, and 32 (26.9%) had grade 3 or higher lipase; 10 (8.4%) of patients had grade 3 or higher elevations of both enzymes (Table 1). Among all patients, there were two cases (1.7%) of pancreatitis (8), representing 20% of patients with grade 3 or higher amylase, 6.3% of patients with grade 3 or higher lipase, and 20% of patients with grade 3 or higher elevations of both enzymes.

Patient A developed fever, nausea, and vomiting a week after completing her fourth dose, which resolved after seven days. She presented to clinic one week later with new grade 3 amylase and grade 4 lipase. A computerized tomography (CT) scan did not show evidence of pancreatitis. Her next immunotherapy dose was delayed for three weeks until her laboratory values normalized. She was treated with nivolumab monotherapy and subsequently had recurrence of asymptomatic grade 2 lipase.

Patient B was noted to have grade 4 lipase and grade 2 amylase associated with diarrhea after his second dose. His colitis was treated with prednisone and infliximab. Six weeks later, after immunosuppression was discontinued, he presented with abdominal pain and grade 4 elevations of lipase and amylase. A CT scan was negative for pancreatitis. He was treated with oral steroids with resolution of his symptoms. His enzymes normalized, and he was rechallenged with pembrolizumab. After two doses, Patient B again developed grade 4 lipase and grade 3 amylase associated with abdominal pain and imaging consistent with pancreatitis. He was restarted on steroids, with resolution of his symptoms. Immunotherapy was discontinued.

As required by protocol, 12.6% of patients had a dose of immunotherapy held and 7.6% of patients received oral steroids for elevations in amylase or lipase with no subsequent pancreatitis. Only Patient B had grade 3 or higher elevation in amylase and/or lipase prior to developing pancreatitis.

The etiology of amylase and lipase elevations often remains unclear as they are nonspecific and may be elevated because of other causes, including neoplasms, surgery, renal failure (9), bowel obstruction, diabetic ketoacidosis (10), HIV (11), and celiac disease. People may also have fluctuating elevations in the absence of other organ dysfunction (12). In patients treated with immunotherapy, elevations in amylase and lipase may reflect T-cell-mediated inflammation even of nonpancreas organs that produce these enzymes. Subclinical inflammation may contribute to the development of delayed sequelae, such as pancreatic exocrine insufficiency, diabetes, or oral mucosal toxicity.

We cannot exclude the possibility that holding immunotherapy and occasionally using steroids in the setting of asymptomatic enzyme elevations minimized subsequent pancreatitis. Nonetheless, given the low incidence of pancreatitis and the discrepancy between laboratory abnormalities and clinical pancreatitis, our clinical practice is to only evaluate amylase and lipase in patients who are clinically suspected to have pancreatitis. Although this is the largest experience yet reported for this irAE, we acknowledge that our description is limited by the relatively small number of patients and retrospective design, which may have led to underreported symptoms.

The NCI recently decided to modify the CTCAE criteria for amylase and lipase. In CTCAE v5.0, grade 4 amylase and lipase now require values exceeding 5X ULN associated with symptoms. Grade 3 amylase and lipase remain independent laboratory toxicities outside of a relevant clinical condition. Given that grade 3 AEs are considered DLTs in many clinical trials, this may have further ramifications as novel immuno-oncology agents are tested, potentially limiting access to

Table 1. Rate of grade 3–4 amylase and lipase elevations, clinical pancreatitis events, steroid usage, and patients who had dose delays for elevated amylase or lipase

Immune-related adverse events	CA209004 (n = 39) No. (%)	CA209069 (n = 16) No. (%)	CA209218 (n = 64) No. (%)	Total (n = 119) No. (%)
Grade 3 amylase	4 (10.3)	0	3 (4.7)	7 (5.9)
Grade 4 amylase	0	0	3 (4.7)	3 (2.5)
Grade 3 lipase	6 (15.4)	3 (18.8)	14 (21.9)	23 (19.3)
Grade 4 lipase	5 (12.8)	0	4 (6.3)	9 (7.6)
Grade ≥3 amylase + lipase	4 (10.3)	0	6 (9.8)	10 (8.4)
Pancreatitis	1 (2.6)	0	1 (1.6)	2 (1.7)
Steroid treatment for asymptomatic elevated amylase/lipase	5 (12.8)	0 (0)	4 (6.3)	9 (7.6)
Dose delay for asymptomatic elevated amylase/lipase	6 (15.4)	1 (6.25)	8 (12.5)	15 (12.6)

effective new therapies. All stakeholders should continue to reevaluate the criteria of the CTCAE in categorizing irAE and determining DLTs in the context of our growing collective clinical experience.

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References

1. U.S. Department of Health and Human Services NIH, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed May 13th, 2016. Published June 14th, 2010.
2. Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med*. 2013;369(2):122–133.
3. Long GV, Atkinson V, Cebon JS, et al. Pembrolizumab (pembro) plus ipilimumab (ipi) for advanced melanoma: Results of the KEYNOTE-029 expansion cohort. *ASCO Meeting Abstracts*. 2016;34(15 suppl):9506.
4. Hellmann MD, Gettinger SN, Goldman JW et al. CheckMate 012: Safety and efficacy of first-line (1L) nivolumab (nivo; N) and ipilimumab (ipi; I) in advanced (adv) NSCLC. *ASCO Meeting Abstracts*. 2016;34(15 suppl):3001.
5. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015;373(1):23–34.
6. Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *N Engl J Med*. 2015;372(21):2006–2017.
7. Hofmann L, Forschner A, Loquai C, et al. Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. *Eur J Cancer*. 2016;60:190–209.
8. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: Revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013;62(1):102–111.
9. Cote GA, Gottstein JH, Daud A, et al. The role of etiology in the hyperamylasemia of acute liver failure. *Am J Gastroenterol*. 2009;104(3):592–597.
10. Yadav D, Nair S, Norkus EP, et al. Nonspecific hyperamylasemia and hyperlipasemia in diabetic ketoacidosis: Incidence and correlation with biochemical abnormalities. *Am J Gastroenterol*. 2000;95(11):3123–3128.
11. Argiris A, Mathur-Wagh U, Wilets I, et al. Abnormalities of serum amylase and lipase in HIV-positive patients. *Am J Gastroenterol*. 1999;94(5):1248–1252.
12. Gullo L. Day-to-day variations of serum pancreatic enzymes in benign pancreatic hyperenzymemia. *Clin Gastroenterol Hepatol*. 2007;5(1):70–74.