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Case Report

Enterocolitis Due to Nivolumab Treated by Infliximab

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Abstract

Immune checkpoint inhibitors are monoclonal antibodies that target CTLA-4 and PD-1. They have proven efficient, either as monotherapy or in combination in several cancer types, resulting in an increase in the incidence of relates side effects.

In this report, we describe a case of a patient with lung cancer treated with nivolumab presenting diarrhea and abdominal pain. Colonoscopy was performed revealing pancolitis mimicking ulcerative colitis [UC]. Treatment was in accordance with UC therapy which resulted in beneficial outcomes.

Severe acute colitis is among the commonest form of gastrointestinal immune-related adverse events due to immune check point inhibitors. Gastroenterologists will be increasingly faced with these patients.

Keywords: Immune-Checkpoint Inhibitors; Colitis; Nivolumab

Introduction

Immune checkpoint inhibitors [ICPI], such as ipilimumab [anti-cytotoxic T-lymphocyte antigen-4 [CTLA-4] antibody] and nivolumab or pembrolizumab [anti-programmed cell death protein-1 [PD-1] antibodies], improve survival in several cancer types. Since inhibition of CTLA-4 or PD-1 leads to non-selective activation of the immune system, immuno-related adverse event [irAE] may affect the skin [rash, vitiligo, exacerbation of psoriasis], glands endocrine [pituitary insufficiency, thyroidis], kidney, joints, liver [immune-hepatitis] and intestine [1]. Support undesirable effects of cancer immunotherapy is the subject of ESMO recommandations [2].

Observation

A 53-year old woman with non-small cell lung cancer stage IV was treated with nivolumab with twice a month infusion 3mg/kg. After the eigth infusion of nivolumab, she manifested abdominal cramps and bloody diarrhea. Bacterial cause for diarrhea was ruled out by means of stool cultures and *Clostridium difficile* toxin tests. Nivolumab was discontinued after onset of grade 3 diarrhea [3]. The laboratory test results were as follows: white blood cell count 11370/µL, hemoglobin level 9,1 g/dL, albumin level 3,9g/dL and C-reactive protein level 63mg/L. Colonoscopy showed reddish, edematous mucosa, exsudate, sequential loss of vascular pattern, erosions type Mayo 2 inflammatory index throughout the entire colorectum, the ileum appearing healthy. Histopathologic examination of biopsy specimen showed active colitis involving infiltration of neutrophils, eosinophils, plasma cells with crypt abscesses.

Base on these findings, we diagnosed the patient as having nivolumab-induced colitis. The patient was initially treated with corticosteroids in accordance with international recommendations for treatment of IPCI-induced enterocolitis [4,5], including intravenous administration of methylprednisolone 1000mg/d for 3 days, followed by oral prednisolone (60mg/d) for 2 weeks. However, the steroid therapy was ineffective. We therefore started intravenous administration of infliximab (5mg/kg), with resulted in resolution of symptoms after the third perfusion and continuation of prednisolone (10mg/d).

After one year the cancer was in remission, but the patient had sometimes bloody diarrhea [grade1] and the recto sigmoidoscopy showed net improvement with reddish and edematous mucosa [Mayo 1 index]. The patient was treated symptomatically with mesalazine orally (4g/d) in the long term. She needed also L thyroxin, hydrocortisone and mineralocorticoids for thyroidis and hypohysitis.

Discussion

Diarrhea and colitis have been previously documented as gastrointestinal tract-related side effects of ICPI. Although PD-1/PD-L1 inhibitors produce fewer side effects than CTLA-4 inhibitors and gastrointestinal toxicity anti-PD-1 is less known [6,7]. A recent series shows that it is much rarer than the observed toxicity with anti-CTLA-4 [8]: it is estimated that 1,5% of patients have enterocolitis induced by anti-PD-1. One half of the patients who were suspects to have gastrointestinal toxicity to anti-PD-1 had this disease [8].

The main differential diagnosis is tumor-related digestive tract: peritoneal carcinomatosis, metastase of lung cancer. Gastrointestinal toxicity anti-PD-1 can make different clinical arrays: acute colitis similar to those observed with anti-CTLA-4, microscopic colitis [lymphocytic or collagenous], inflammation of the upper digestive tract, pseudo obstruction [9].

Three out of four patients respond to corticosteroids [10]. However, the moderate duration of symptoms is 90 days, relapses to arrest and/or decrease doses of corticoids are common [9]. Mesalazine could represent first -line treatment intention in mild proctitis [11]. Corticoids enable a sustainable remission in a two out of three patients [12,13]. Second treatment intention, after primary failure or loss of response to corticoids, like our patient, is the infliximab. One or two injections are enough generally to obtain the remission [14]. Infliximab does not seem to aggravate the cancer [10]. Some patients have to be operated on a colectomy because of complications [abscesses, toxic maceration, perforation]. A recent serie shows that partial colectomies are associated with inflammation of the colon, causing postoperative complications [13]. Berggvist., *et al.* report on seven patients with ICPI-induced enterocolitis, which were either corticosteroid-dependant and/or partially refractory, managed successfully with vedolizumab infusions [15]. They consider suitable for vedolizumab treatment patient with steroid dependant and/or partially refractory mild to moderate enterocolitis and without irAE. In contrast, patient with severe gut inflammation that demands urgent measures should be considered for other therapies such as infliximab, mycophenate mofetil [16] or, as last resort, colectomy.

The duration of intestinal inflammation is not known precisely. Several patients had a colonoscopy of control several months after the first symptoms [13]. Endoscopic and/or histological lesions were observed in about one in two patients.

We schematize the behavior to hold in the presence of nivolumab-induced colitis as follows: stop of anti-PD-1, methylprenisolone 0,8 to 2mg/kg and 24 hours medicosurgical monitoring. We make the point between d3 and d7. The answerers corticosteroids intravenous go to oral corticosteroids, with a gradual decrease over 8 to 12 weeks. One-third to two-thirds of patients do not respond to corticosteroids intravenous or relapse during dose reduction of corticoids per os. They come under treatment by infliximab 5mg/kg indeed 10m/kg. A few patients may require a second injection, one to two weeks after the first [4].

In a recent study on 254 melanoma patients with irAE, 29 [11,4%] patients received infliximab therapy and high-dose corticosteroids [17]. Among these 29 patients, 21 patients responsed to infliximab but 8 [27,6%] did not respond and received prolonged courses of corticosteroids.

There is very little data available on the effects and safety of infliximab treatment in this context and on the potential effects of corticosteroids in combination with infliximab on the anti-tumor efficay of ICPI therapy [18]. In a retrospective study on ipilimumab-treated melanoma patients who had developed diarrhea, there was no significant difference in the median overall survival time between those treated with infliximab or not [10]. There is an ongoing debate whether irAE and/or the severity of irAE is associated with better cancer-specific outcomes, and whether treatment with immunosuppressive agents potentially counteracts the anti-tumor effect of ICPI therapy. There are several studies supporting these concepts [10,19] but also those refuing them [5,17].

It is not surprising that anti-CTLA-4 are the cause of enterocolitis. In fact, the germinal mutations of the CTLA-4 are at the origin of inflammatory diseases which can reach the lung, the brain, but also the intestine, in the majority of the cases [20,21]. Regulatory T cells FOXP3+ of the intestine are generated locally from precursors that express receptors specific to microbota antigens [22]. Several recent animal [23,24] and human [25,26] studies have demonstrated a link between ICPI therapy response, gut microbiota composition and intestinal inflammation.

Conclusion

There are several new ICPI agents being subjected to clinical evaluation in numerous types of malignancies resulting in an increase in the incidence of related side effects, and subsequently the prevalence of ICPI induced-enterocolitis may be expected to increase.

It is important to develop evidence-based optimized immune mediated-adverse effects management algorithms, taking the long term cancer-treatment strategy and the overall survival into account.

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