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Original Article

Evaluation of Immune Checkpoint Inhibitor-Associated High-Grade Colitis/Diarrhea Frequency and Management

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Abstract

Objective: Immune checkpoint inhibitors are an increasingly important treatment option in cancer treatment; however, potential immune-related adverse events are one of the main factors limiting the use of the treatment and colitis/diarrhea is one of them. Data about this side effect were derived from clinical trials, and articles examining this side effect in real life are limited. We evaluated the frequency and management of colitis and diarrhea in cancer cases treated with an immune checkpoint inhibitor.

Methods: A total of 363 oncology patients treated with immune checkpoint inhibitors at Hacettepe University Oncology Hospital were evaluated retrospectively between October 2014 and November 2021. Grade 3 and higher colitis/diarrhea cases were detected in3 7 patients, and clinical properties were reviewed in detail.

Results: Of these 7 patients, 3 of them were diagnosed with renal cell carcinoma, 2 with lung adenocarcinoma, 1 with malignant melanoma, and 1 with endometrial cancer. Three patients were treated with nivolumab, 1 with pembrolizumab, 1 with atezolizumab, and 2 with nivolumab–ipilimumab combined therapy. The colitis/diarrhea occurred approximately at the end of the second month of treatment. Immunotherapy was discontinued in 6 patients. All patients were treated with steroids, and none of them needed non-steroid immunosuppressive drugs.

Conclusion: In our study, the rate of diarrhea/colitis of grade 3 and above was 2%, similar to other clinical trials. Although our patient population is small, the development of colitis in 2 patients receiving combined immune control inhibitors is remarkable. Close follow-up of patients under treatment regarding side effects protects them from possible complications with early intervention.

Keywords: Adverse events, colitis, diarrhea, immunotherapy

INTRODUCTION

Cancer immunotherapy is a novel cancer therapy field with increasing importance. Immunotherapy is the activation of the immune system to fight against cancer cells. Anti-programmed cell death protein 1 (PD-1) and anti-T lymphocyte-associated protein 4 (CTLA-4) agents are immune checkpoint inhibitors that are frequently used as a choice of immunotherapy for various cancers.[1] Immune checkpoint inhibitors were first used in the treatment of malignant melanoma, lymphoma, lung cancer, and renal cell carcinoma. In the following years, they showed efficacy in the treatment of different cancers.[1]

Despite its great success in cancer treatment, immune-mediated side effects can be seen due to the overactivation of the immune system. Fatigue, skin involvement, pneumonitis, colitis, hepatitis, and endocrinopathy, especially hypophysitis and thyroiditis, can be secondary side effects of immune checkpoint inhibitors.[2]

The immunotherapy-related side effects are evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0. For example, the most common side effect diarrhea can be evaluated according to CTCAE v5.0; number of stools <4 per day is classified as grade 1, 4-6 stools are grade 2, 7, and above stools are grade 3, life-threatening diarrhea is grade 4; asymptomatic colitis is classified as grade 1, abdominal pain or blood/mucus in the stool as grade 2, peritoneal findings as grade 3, and life-threatening colitis is grade 4 adverse event.[3]

Discontinuation of the drug is the most important step in the treatment of immune-mediated colitis; moreover, according to the grading of the adverse events, different agents can be used, from conventional glucocorticoids to biological agents such as infliximab or vedolizumab and immunosuppressive agents, such as cyclophosphamide and mycophenolate mofetil in resistant cases.[4]

Treatment modality is choosen for colitis/diarrhea developing secondary to immune checkpoint inhibitors according to grade of adverse event. In grade 1 patients, symptomatic treatment is given without discontinuing the drug. In grade 2 patients, the drug is discontinued, low-dose steroids

and/or symptomatic treatment are given according to the patient's status, and immune checkpoint inhibitors can be restarted when the patient's complaints regress. In grade 3-4 patients, the drug is permanently discontinued, and steroid treatment is given.[4]

In this case series, we would like to review our cases who are treated with immune checkpoint inhibitors in terms of gastrointestinal adverse events. We retrospectively reviewed and analyzed our patients at Hacettepe University Oncology Hospital between October 2014 and November 2021, which yielded 363 oncology patients. We recorded the patient data, such as age, gender, type of malignancy, a treatment used, treatment cycle that developed colitis/diarrhea, stage of colitis/diarrhea (CTCAE v5.0), and whether or not to discontinue immune checkpoint inhibitor treatment after side effects. A total of 7 patients were identified as having colitis/diarrhea secondary to an immune checkpoint inhibitor therapy. When a patient had diarrhea during an immunotherapy treatment; stool culture, stool amoeba, parasite, Clostridium difficile toxin, and celiac serologic tests were examined; infection and other common diarrhea causes (laxatives, inflammatory bowel disease, hyperthyroidism, etc.) were ruled out and if a biopsy was taken from a patient, Cytomegalovirus (CMV) colitis and celiac disease were ruled out. After excluding all these diagnosis, the diagnosis of immune-associated colitis was made. Since the calprotectin test kit was not found in our hospital, it could not be measured. After excluding other etiologies, diagnosis was made and symptomatic and steroid treatment were given. Here in, we will briefly discuss these cases.

CASE 1

A 66-year-old male patient was first diagnosed with laryngeal cancer in 2018 and was considered cured after radiotherapy. He was diagnosed with lung adenocarcinoma in 2019. After 6 cycles of paclitaxel-carboplatin chemotherapy, atezolizumab treatment was initiated due to the progression of his malignancy. After taking the second cycle, the patient had watery diarrhea 10-15 times a day, which later became bloody. There was mild abdominal pain and no fever. Duration of diarrhea was approximately 10 days. The patient was hospitalized for 1 week for intravenous hydration due to hypovolemia. The rectoscopy showed proctitis that was presumed to be secondary to immunotherapy. The patient's immunotherapy was stopped, and 40 mg methylprednisolone treatment was started with a diagnosis of grade 2 colitis and grade 3 diarrhea according to CTCAE v5.0 secondary to immunotherapy. It was discontinued within approximately 2 months with a gradual reduction scheme reducing the dosage by 5 mg every week with complete resolution of diarrhea.

CASE 2

A 49-year-old female patient with metastatic malignant melanoma was diagnosed in 2008. The patient was followed up with remission after excision, and the recurrence was detected in the right groin in 2015. Interferon and temozolomide treatments were given due to lung metastases. Due to progression after these treatments, the patient received 5 cycles of nivolumab. After detecting newly developing brain metastases, ipilimumab treatment was added to nivolumab treatment. After the second cycle, the patient started to have watery diarrhea 10 times a day and crampy abdominal pain. The patient did not undergo a colonoscopy because the patient refused it. An abdominal computed tomography showed thickening of rectosigmoid colon. Immunotherapy-associated colitis and diarrhea were considered, nivolumab and ipilimumab treatment were stopped, oral rehydration therapy and methylprednisolone were initiated, and gradually discontinued after the patient's diarrhea and abdominal pain ceased. Methylprednisolone dosage and duration of treatment and duration of diarrhea were not found in patient's medical history records.

CASE 3

A 53-year-old female patient with metastatic renal cell carcinoma and hypothyroidism was diagnosed with renal cell carcinoma in 2013 and had lung metastases at the time of diagnosis. Nivolumab treatment was started in 2016 as the patient progressed after interferon treatment. A total of 31 cycles of nivolumab were given to the patient. Due to disease progression, ipilimumab treatment was added to the last 4 cycles of nivolumab. The patient started to have abdominal pain and diarrhea 6-8 times a day after the fourth cycle of nivolumab and ipilimumab treatment. There was no fever. Duration of diarrhea was approximately 2 weeks. A colonoscopy revealed diffuse colitis. Immunotherapy was stopped, and loperamide and methylprednisolone treatment were initiated for immunotherapy-related colitis and diarrhea. Methylprednisolone dosage and tapering scheme were not found in patient's medical history records. Ten months later, the diarrhea was completely diminished.

CASE 4

A 55-year-old male patient with renal cell carcinoma and hypertension underwent a right radical nephrectomy in 2020 for renal cell carcinoma in his right kidney. After the lung metastasis was detected in December 2020, the patient started to take sunitinib. Seven cycles of nivolumab treatment were given after progression was observed in August 2021. After the seventh cycle, the patient developed bloody diarrhea 8-10 times a day, the patient was subfebrile but infection was excluded, duration of diarrhea was approximately 2 weeks. A rectosigmoidoscopy was performed, and the findings were compatible with rectitis. With the diagnosis of immunotherapy-associated colitis, nivolumab treatment was discontinued, the patient was hospitalized for 1 week and IV 40 mg methylprednisolone was started. Grade 3 diarrhea and grade 2 colitis regressed significantly according to CTCAE v5.0 within a week under treatment. The methylprednisolone treatment was completed in 2 months by reducing the dosage by 5 mg every week.

CASE 5

A 68-year-old female patient with metastatic lung cancer was diagnosed in 2019. After 5 cycles of carboplatin-pemetrexed chemotherapy, the patient was started on nivolumab treatment due to the progression detection. The patient received 21 cycles of nivolumab treatment, and a significant improvement in the patient's status was observed. After the sixth cycle of nivolumab, the patient developed bloody diarrhea 4-5 times daily. There was no abdominal pain and fever. A colonoscopy showed distal colitis. Because there was a response to nivolumab treatment, her treatment was continued. Mesalazine treatment was started. At first, the stool number was reduced to 4-5 from 10-11 with mesalazine

MAIN POINTS

- Immune checkpoint inhibitors are an increasingly important treatment option in cancer treatment, but potential immune-related adverse events are one of the main factors limiting the use of the treatment.
- Information about this side effect is derived from clinical trials, and articles examining this side effect in real life are limited.
- Close follow-up of the patients under treatment regarding side effects will help improve their quality of life and protect them from possible complications with early intervention.

but increased later. A rectoscopy was performed, and the biopsy result was again compatible with diffuse active colitis. Nivolumab treatment was discontinued, and paclitaxel and carboplatin were started. About 32 mg methylprednisolone treatment was added to mesalazine, and the patient's diarrhea regressed to 4-5 again. Total duration of diarrhea was more than 4 months. The patient was deceased due to complications unrelated to bowel symptoms during the methylprednisolone treatment with a good response to diarrhea.

CASE 6

A 74-year-old patient with metastatic renal cell carcinoma and hypertension was diagnosed with renal cell carcinoma in 2017. There were metastases in the pancreas and adrenal glands at the time of diagnosis. The patient was started on pazopanib therapy. Pazopanib treatment was discontinued due to progression, and nivolumab treatment was started in May 2018. After the eighth cycle of nivolumab, the patient developed watery diarrhea 10 times a day and abdominal pain. There was no fever. A colonoscopy was not performed due to severe presentation and put on methylprednisolone, loperamide, and ornidazole with the diagnosis of immune-associated colitis. Under treatment, the number of stools decreased to 3-4 per day. Methylprednisolone therapy was discontinued with a dose reduction after the cessation of the symptoms. Methylprednisolone dosage, tapering scheme, and duration of diarrhea were not found in patient's medical history records.

CASE 7

A 51-year-old female patient with recurrent endometrial cancer was diagnosed in May 2019. Since the disease progressed after 6 cycles of carboplatin-paclitaxel, cisplatin was given concurrently with radiotherapy. Pembrolizumab treatment was started in September 2020 because the patient had a recurrence in the follow-up. After the second cycle, there was watery diarrhea 6 times per day and abdominal pain started. There was no blood in stool, or fever. In the colonoscopy, performed in October 2020, the patient had mild colitis. The patient was put on 32 mg methylprednisolone and followed in outpatient clinic. The number of stools decreased from 6-7 to 4-5 times daily. Pembrolizumab treatment was not discontinued due to the response of the patient's malignancy to the treatment. Methylprednisolone treatment was discontinued after 1 month by reducing dosage 8 mg in every week. When the number of stools increased to more than 10 per day again in April 2021, loperamide and mesalazine were started in the patient, and diarrhea decreased to 5-6 times per day. This time colonoscopy was performed, no finding in favor of active colitis was detected, and it was decided to continue symptomatic treatment. The patient took pembrolizumab 27 cycles, and her disease continued to be followed in regression without any bowel symptoms. Total duration of diarrhea was 9 months.

DiscussionImmune checkpoint inhibitors increase the survival time of cytotoxic T cells by inhibiting cytotoxic CTLA-4 and PD-1 receptors on cytotoxic T cells with immune checkpoint inhibitors, and thus the anti-tumor effect is targeted. However, immune-related side effects are observed due to the same mechanism (Table 1).[5]

In the literature, immune checkpoint inhibitor-related colitis incidence differs between the agents used. Severe (grade 3-4) colitis, according to CTCAE v5, is seen in approximately 3% of those using anti-PD-1, 6% of those using anti-CTLA-4, and 9% of those receiving dual anti-PD-1 and anti-CTLA-4. [6] Incidence of severe (grade 3-4) diarrhea, according to CTCAE v5, is highest with combined therapy (9.2%) and again is higher with anti-CTLA (7.9%) than anti-PD-1 (1.3%) and anti-PD-L1 (0.3%).[7]

In a study, in which colonic biopsies from patients with anti-CTLA4 induced colitis and anti-PD-1 induced colitis, it was found that CD8+ T cells were found in the lamina propria and epithelium in anti-PD-1-induced colitis, whereas CD4+ T cells were found in anti-CTLA-4-induced colitis. These findings may explain why immunotherapy-related colitis and diarrhea are more common with anti-CTLA 4 than anti-PD1 and anti-PDL1.[8]

Approximately 2/3 of patients respond to steroid treatment.[9] If the case is steroid resistant, infliximab, an anti-TNF inhibitor, can be given as a single dose. Rarely if the cases are resistant to infliximab, the alpha4-beta7 integrin inhibitor vedolizumab can be used.[4]

There were 363 patients at Hacettepe University Oncology Hospital using immune checkpoint inhibitors. The mean age of these patients

Table 1. Patients with Immunotherapy-Associated Colitis/Diarrhea

Case Number	Age	Sex	Malignancy Type	Immunotherapy Used	Immunotherapy Cycle Developing Colitis/Diarrhea	Grade of Side Effect	Colitis/Diarrhea Treatment	Whether İmmunotherapy Was Discontinued
Case 1	66	Male	Lung adenocarcinoma	Atezolizumab	Second cycle	Grade 3	Steroids	Yes
Case 2	49	Female	Malignant melanoma	Nivolumab + ipilimumab	Seventh nivolumab cycle + 2nd ipilimumab cycle	Grade 3	Steroids	Yes
Case 3	53	Female	Renal cell carcinoma	Nivolumab + ipilimumab	Thirty-first nivolumab cycle + 4th ipilimumab cycle	Grade 3	Steroids	Yes
Case 4	55	Male	Renal cell carcinoma	Nivolumab	Seventh cycle	Grade 3	Steroids	Yes
Case 5	68	Female	Lung adenocarcinoma	Nivolumab	Sixth cycle	Grade 3	Steroids + mesalazine	Yes
Case 6	74	Male	Renal cell carcinoma	Nivolumab	Eighth cycle	Grade 3	Steroids + loperamide + ornidazole	Yes
Case 7	51	Female	Endometrial cancer	Pembrolizumab	Second cycle	Grade 3	Steroids + mesalazine + metronidazole	No

was 59.4 years. A total of 3 of them were diagnosed with renal cell carcinoma, 2 with lung adenocarcinoma, 1 with malignant melanoma, and 1 with endometrial cancer.

A total of 19 patients took ipilimumab, 34 patients took pembrolizumab, 40 patients took atezolizumab, 246 patients took nivolumab, 16 patients took combined immunotherapy, and 8 patients took more than 1 immunotherapy at different times. Immune-associated colitis was seen in 7 (%1.92) of all patients. A total of 3 patients (1.21%) were treated with nivolumab, 1 (2.94%) with pembrolizumab, 1 (2.5%) with atezolizumab, and 2 (12.5%) with nivolumab–ipilimumab combined therapy. The colitis/diarrhea side effect occurred after an average of 4.4 cycles, approximately at the end of the second month of treatment. Endoscopic imaging was performed in 5 of 7 patients, and the patients were evaluated as having grade 2 colitis. Two patients who did not undergo colonoscopy were evaluated as grade 1 because of diarrhea accompanied by abdominal pain and the absence of peritoneal findings. Most of the patients were accompanied by grade 2-3 diarrhea. Patients were treated with steroids and symptomatic therapy. Again, full/partial response to steroid treatment was achieved in all patients, and none of the patients needed to use infliximab.

When we compare our data with the literature, the incidence of colitis with anti-PD-1 and anti-PD-L1 is lower, because there was no colitis with anti-CTLA-4, we cannot compare it with the literature, the incidence of colitis with combined therapy is higher. As mentioned above, in the literature around one-third of patients are resistant to steroid treatment[9] but in our case series, all patients responded to steroid treatment.

One of the weaknesses of our case series could be possible missed data, such as methylprednisolone dosage tapering scheme and diarrhea characteristics due to the retrospective nature of the study. The second one is that since our patient population is relatively small, small changes may affect statistics significantly. Also, calprotectin was not measured in our hospital, so we could not use it in diagnosis and follow-up.

As a result, patients taking immune checkpoint inhibitors, which are preferred in treating many malignancies, should be followed up with caution regarding colitis secondary to treatment, which can significantly reduce the quality of life. If colitis/diarrhea develops, it should be intervened in the early period.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of İstinye University, (Approval No: 2017-KAEK-120, 3/2022.G-87).

Informed Consent: Written informed consent was obtained from all atrial fibrillation and control group patients participating in the study.

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