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Risk Factors and Prognostic Analysis of Immune Checkpoint Inhibitor-Related Colitis in Lung Cancer

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Objective: This study aimed to investigate the risk factors for immune checkpoint inhibitor (ICI)-related colitis and its impact on prognosis in the treatment of lung cancer.

Methods: This retrospective, single-center, observational study included lung cancer patients who received ICIs treatment between January 2016 and January 2022. The correlation between immune-related colitis and prognosis was evaluated. Kaplan-Meier analysis was used to compare the median overall survival (OS).

Results: Among the lung cancer patients treated with ICIs, the incidence of colitis was 5.88% (35/595). The severity of colitis was graded as follows: grade 1 (8 cases), grade 2 (15 cases), grade 3 (9 cases), and grade 4 (3 cases). Except for the 1 case that resulted in death due to grade 4 adverse events, the remaining patients showed significant improvement after corticosteroid intervention. Among the 35 patients with ICI-related colitis, complete remission was not achieved. Partial remission was observed in 11 cases, disease stability in 16 cases, disease progression in 7 cases, and death in 1 case. Among the included patients, 19 chose to continue ICI treatment after symptom relief. The overall survival for all participants was 34 months (IQR: 24–36), while the overall survival for those who received ICI treatment again was 36 months (IQR: 32-NA), and for those who did not receive ICI treatment again was 32 months (IQR: 21–35). Kaplan-Meier survival curve analysis showed that patients who received ICI treatment again had significantly better overall survival compared to other patients.

Conclusion: Immune-related colitis remains a significant concern in lung cancer patients treated with ICIs and requires close monitoring and timely intervention. Restarting treatment after symptom relief can provide additional benefits for patients.

Keywords: lung cancer, immune checkpoint inhibitors, colitis, risk factors, prognosis

Introduction

Lung cancer is a prevalent malignancy characterized by its high invasiveness and metastatic potential. Conventional treatments, such as surgical resection, radiation therapy, and chemotherapy, have limited efficacy and often entail significant adverse effects.[1] Non-small cell lung cancer (NSCLC) represents the most common subtype, with over 50% of patients being diagnosed at an advanced stage and a dismal 5-year survival rate of merely 5%.[2] Standard therapies, including chemotherapy and radiation, typically yield moderate responses in patients with metastatic NSCLC, with 5-year survival rates ranging from 6% to 30%.[3]

Immune checkpoint inhibitors (ICIs) have emerged as a novel class of antineoplastic agents, harnessing the immune system to combat tumor cells by inhibiting immune checkpoint molecules—negative regulators found on the surface of T cells that hamper their activation and proliferation.[4] In recent years, the advent of ICIs has revolutionized the prognosis of various malignancies. Monoclonal antibodies targeting programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) have demonstrated remarkable antitumor

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activity by selectively activating T cells and suppressing the immune system.[5] Notably, the KEYNOTE-021 study revealed that the combination of chemotherapy and pembrolizumab achieved an impressive efficacy rate of 55% in treating NSCLC, significantly surpassing the 29% observed in the chemotherapy-alone arm, while simultaneously reducing the risk of disease progression by 47%.[6]

The employment of ICIs has revolutionized the survival outcomes of NSCLC patients, exhibiting a more favorable toxicity profile compared to traditional chemotherapy.[7] Nevertheless, ICIs may also elicit immune-related adverse events (irAEs), including gastrointestinal symptoms such as abdominal pain, diarrhea, hematochezia, nausea, and vomiting. Severe cases may manifest with fever, dehydration, electrolyte imbalances, and other life-threatening complications. Although the incidence of organ-specific irAEs remains relatively low, the utilization of ICI agents heightens the risk of such events as opposed to standard therapies.[8] Notably, immune checkpoint inhibitor-associated colitis represents a predominant irAE, frequently necessitating treatment interruption, permanent discontinuation, and even resulting in treatment-related mortality.[9] Inadequate management and timely intervention for ICI-related colitis in clinical practice can culminate in treatment cessation, failure, and egregious consequences for patients.[10] Consequently, it becomes imperative for clinicians to gain a comprehensive understanding of the distinct clinical features and prognostic implications associated with ICI-related colitis linked to anti-PD-1/PD-L1 antibodies, anti-CTLA-4 antibodies, and the combination of anti-PD-1 and anti-CTLA-4 antibodies.

Therefore, the present study aims to elucidate the disparities in clinical characteristics and prognostic outcomes between ICI-related colitis associated with anti-PD-1/PD-L1 antibodies, anti-CTLA-4 antibodies, and the combination of anti-PD-1 and anti-CTLA-4 antibodies.

Materials and Methods

Study Design

This study is a single-center, retrospective, observational study that included 595 patients with lung cancer who received ICIs treatment at our hospital from January 2016 and January 2022. Clinical information and demographic data of the patients were collected, and patient survival status was obtained through telephone follow-up.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) Age between 18 and 80 years old; (2) Patients with histologically confirmed stage III–IV lung cancer, including non-small cell lung cancer and small cell lung cancer; (3) Patients who received ICI treatment and had imaging reports available for evaluating treatment response; (4) Receive at least 1 cycle of ICI therapy, either as first- or second-line therapy.

Exclusion criteria: (1) Patients with concurrent other malignancies; (2) Patients with incomplete clinical data; (3) Patients who did not undergo regular evaluation of treatment response at our hospital.

Diagnosis, Grading and Treatment of ICI-Related Colitis

Diagnosis of ICI-related colitis:[11] The diagnosis requires a comprehensive consideration of the patient's symptoms, colonoscopic examination, and pathological examination results, while excluding other possible causes. (1) Clinical symptoms: Patients present with symptoms of colitis such as abdominal pain, diarrhea, rectal bleeding, and constipation. (2) Colonoscopic examination: Findings include mucosal congestion, loss of vascular pattern, erosion, and ulcer formation. The lesions can be diffuse or segmental, often involving the left half of the colon. Histopathological images often show features of acute colitis, such as neutrophil and eosinophil infiltration, as well as features of chronic inflammatory bowel disease, such as mononuclear and neutrophilic infiltration and crypt architectural abnormalities. (3) Pathological examination: Biopsy tissue examination confirms the inflammatory reaction of the colonic mucosa and excludes other causes. (4) Exclusion of other causes: Other causes of colitis, such as infectious colitis and intestinal tumors, should be excluded. (5) History of immunotherapy drug use: The occurrence of symptoms is correlated with the history of immunotherapy drug use.

Grading of ICI-related colitis:[12] G1: Increase in daily bowel movements of less than 4 compared to baseline; G2: Increase in daily bowel movements of 4–6 compared to baseline, or accompanied by abdominal pain or mucous bloody stools; G3: Increase in daily bowel movements of more than 7 compared to baseline, or severe or persistent abdominal pain, rectal bleeding, and fever; G4: Patients present with life-threatening clinical conditions requiring urgent intervention (such as hemodynamic abnormalities, intestinal perforation, bleeding, ischemic colitis, toxic megacolon).

Treatment of ICI-related colitis. For mild symptoms (G1), conservative treatment with antidiarrheal drugs is usually used. Moderate to severe symptoms (G2 or above) are usually treated with systemic corticosteroids (eg, prednisone). Continue glucocorticoids for at least 4 to 6 weeks after symptom remission.

Restart of ICI

Combined with the SITC and ASCO recommendations, the following policies are specified for restarting the ICI. One is when the corticosteroid dose is reduced to ≤10 mg/day and the patient is asymptomatic; The second is for grade 3 colitis, consider permanently stopping the CTLA-4 drug, while the PD-1 or PD-L1 drug can be restarted when the patient recovers to grade 1 or below. Of course, informed consent is required before restarting treatment.

Outcome Measures

Clinical efficacy

The clinical efficacy of patients was evaluated according to the efficacy evaluation criteria for solid tumors (RECIST 1.1), which were divided into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). CR was defined as the disappearance of all target lesions with no new lesion. PR was defined as at least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD), taking as reference the smallest sum diameters while on study. PD was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study).

Risk factor analysis

The incidence, severity, and treatment outcomes of ICI-related colitis were recorded to explore the risk factors associated with its occurrence.

Prognostic analysis

All patients were followed up until June 30, 2023, with monthly follow-ups. Overall survival (OS) was recorded, and a comparison of OS between groups with and without ICI-related colitis was performed.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics for Windows Version 25.0 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as frequencies or percentages and analyzed using Pearson's chi-square test or Fisher's exact test. Continuous variables were presented as means and standard deviations and compared between groups using Student's *t*-test or Mann–Whitney *U*-test for paired comparisons. OS was calculated from the start of the first ICI cycle until the date of death from any cause, and the follow-up duration was evaluated using the Kaplan-Meier method. All hypothesis tests were two-tailed, and a p-value < 0.05 was considered statistically significant.

Results

Incidence of ICI-Related Colitis

A total of 35 cases of ICI-related colitis were identified. Of these cases, 25 were male and 10 were female, with an age range of 41 to 79 years and a mean age of 62.36 ± 14.19 years. The histological types included 18 cases of adenocarcinoma, 11 cases of squamous cell carcinoma, and 6 cases of other types. ECOG performance status scores were 0 in 5 cases, 1 in 13 cases, 2 in 14 cases, and 3 in 3 cases. The duration of ICIs drug application was 57 days

Table 1 Incidence of ICI-Related Colitis in 35 Cases

Characteristics (n = 35)	n	(%)
Age of ICIs(yrs)		
Mean, SD	62.36, 14.19	
Median (IQR)	65 (57–79)	
Sex		
Male	25	71.43
Female	10	28.57
Histological types		
Adenocarcinoma	18	51.43
Squamous cell carcinoma	11	31.43
Others	6	17.14
ECOG score		
0	5	14.29
1	13	37.14
2	14	40.00
3	3	8.57
Duration of ICIs drug application (d)		
Median (IQR)	57 (20~92)	
Treatment lines		
First-line treatment	28	80.00
Second-line or higher treatment	7	20.00
Number of distant metastases		
<3	20	57.14
≥3	15	42.86

(interquartile range: 20–92 days). Among the treatment lines, 28 cases received first-line treatment, and 7 cases received second-line or higher treatment. Twenty cases had fewer than 3 distant metastases, while 15 cases had 3 or more distant metastases. The basic characteristics of ICI-related colitis are shown in Table 1.

Symptoms and Signs of ICI-Related Colitis

Among the cases of ICI-related colitis, there were 8 cases of grade 1, 15 cases of grade 2, 9 cases of grade 3, and 3 cases of grade 4. All patients with ICI-related colitis experienced diarrhea, with a maximum frequency of 15 times per day. Abdominal pain was present in 16 cases, and 24 cases had mucous bloody stools. The symptoms and signs of ICI-related colitis are shown in Table 2.

Table 2 Symptoms and Signs of ICI-Related Colitis

Characteristics (n = 35)	n	(%)
Grade		
G1	8	22.86
G2	15	42.86
G3	9	25.71
G4	3	8.57
Symptoms and signs		
Diarrhea	35	100.00
Abdominal pain	16	45.71
Mucous bloody stools	24	68.57

Table 3 Efficacy of Patients with ICI-Related Colitis

Characteristics (n = 35)	n	(%)
Complete remission	0	0.00
Partial remission	11	31.43
Stable disease	16	45.71
Progressive disease	7	20.00
Death	1	2.86

Survival of Patients with ICI-Related Colitis

Among the 35 cases of ICI-related colitis, there was no complete response to lung cancer. Partial remission was observed in 11 cases, disease stability in 16 cases, disease progression in 7 cases, and death in 1 case. The clinical outcomes of ICI-related colitis are shown in Table 3.

Management and Prognosis of Patients with ICI-Related Colitis

Among the 35 cases of ICI-related colitis, 35 cases showed relief of colitis symptoms after discontinuation of the therapy and administration of corticosteroids. One case died due to grade 4 adverse events. Among the 34 surviving patients, 19 chose to continue ICI treatment after complete colitis recovery incorporate the patient's personal wishes, including 6 cases of grade 1 and 13 cases of grade 2 ICI-related colitis. The patients were followed up monthly after surgery to obtain survival information, with a median follow-up duration of 22 months (interquartile range: 15–30 months). The overall survival for all participants who received ICI treatment again was 34 months (interquartile range: 24–36 months), with a total survival of 36 months (interquartile range: 32-NA months) for those who received ICI treatment again and 32 months (interquartile range: 21–35 months) for those who did not receive ICI treatment again. Kaplan-Meier survival curve analysis showed that the overall survival benefit of patients who received ICI treatment again was significantly better than that of other patients, as shown in Figure 1.

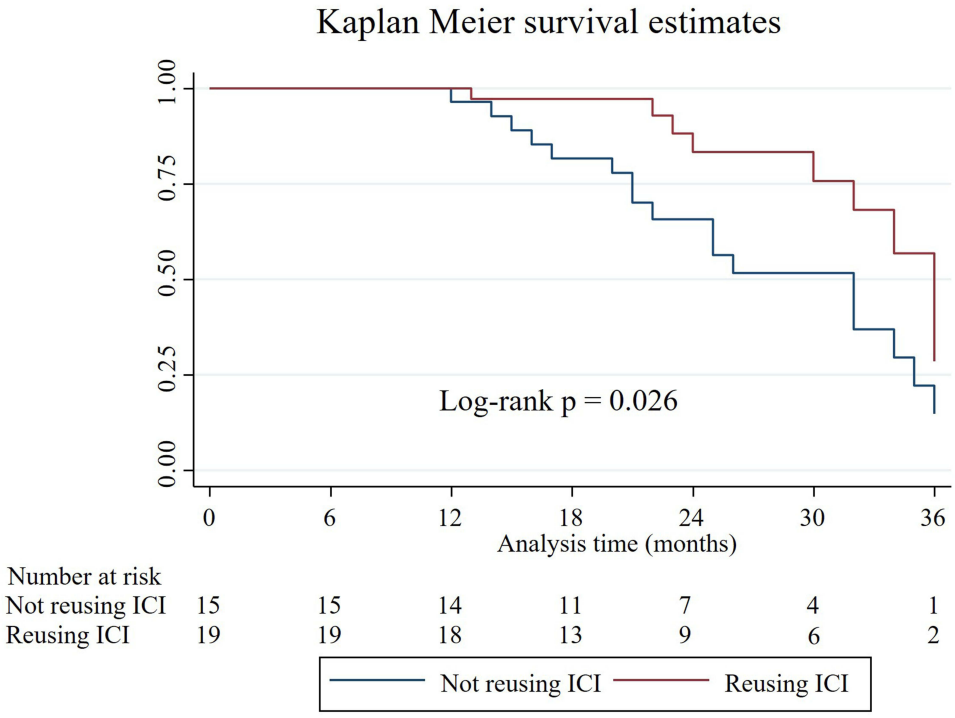

Figure 1 Kaplan-Meier survival curve.

Discussion

The results of this study indicate that the incidence of colitis in lung cancer patients treated with ICIs was 5.88% (35/595). Based on severity, colitis was classified into five grades (G1-G5), with 8 cases classified as grade 1, 15 cases as grade 2, 9 cases as grade 3, and 3 cases as grade 4. Except for the 1 case that resulted in death due to grade 4 adverse events, the remaining patients showed significant improvement after corticosteroid intervention. ICIs are a novel class of anti-cancer drugs that enhance the activity of T lymphocytes by blocking the interaction between CTLA-4 and PD-1/PD-L1 receptors, thereby activating the immune system to recognize and eliminate tumor cells that have evaded the immune response.[13] However, due to the presence of homologous antigens or antigenic epitopes in normal tissues and tumor cells, activated T cells can also cause immune damage to normal tissues, leading to irAEs of varying degrees in different organ systems, including the skin, mucous membranes, thyroid, gastrointestinal tract, liver, lungs, and heart. These events can result in treatment discontinuation, and in severe cases, can be life-threatening.[14] The colon is one of the common target organs for adverse events, with clinical manifestations such as diarrhea and colitis.[15] Early recognition of ICI-related colitis is crucial for clinicians. Patients who are currently or previously treated with ICIs, especially within 5–10 weeks of treatment initiation, should be highly vigilant for symptoms such as diarrhea or colitis that may indicate ICI-related colitis.[16] The incidence of colitis is highest with CTLA-4 inhibitors, with a reported incidence of 7.7% and a rate of grade 3 or higher colitis of 5.7%.[17] The incidence in this study was 5.88%, with a rate of grade 3 or higher colitis of 2.02% (12/595), which is consistent with previous studies. It is important to note that colitis may be caused by non-immune reactions to drugs or disease progression. In addition to routine tests such as complete blood count, liver and kidney function, and erythrocyte sedimentation rate, stool pathogen testing should be performed to carefully exclude colitis caused by bacteria, fungi, or other pathogens, and colonoscopy may be necessary when indicated.[18] A meta-analysis of 21 studies confirmed that the incidence of colitis after ICI treatment was 2.3%, and the incidence of high-grade colitis was significantly higher than that in non-ICI-treated patients, supporting the risk of colitis associated with ICIs.[19]

In this study, among the 35 patients with ICI-related colitis, complete remission was not achieved. Partial remission was observed in 11 cases, disease stability in 16 cases, disease progression in 7 cases, and death in 1 case. Studies have shown that gastrointestinal toxicity is associated with higher survival rates and treatment outcomes compared to other patients receiving immunotherapy. Patients with adverse events have a good and durable response to immunotherapy, which is associated with longer overall survival, possibly due to the activation of the immune system against cancer reflected by immune-related events.[20] In this study, among the 42 patients who chose to continue ICI treatment after symptom relief, the overall survival was 36 months (IQR: 32-NA) for those who received ICI treatment again and 32 months (IQR: 21–35) for those who did not receive ICI treatment again. Kaplan-Meier survival curve analysis showed that the overall survival benefit of patients who received ICI treatment again was significantly better than that of other patients.[21] Regarding restarting treatment, ICI therapy should be discontinued in cases of grade 3 colitis after weighing the risks and benefits, and ICI therapy should be permanently discontinued in cases of grade 4 colitis. In addition, studies have shown that restarting ICI may lead to recurrence of colitis in some cases. For example, one study found that three-quarters of patients who received ipilimumab again after entering colitis remission had a relapse. There is currently no evidence-based medicine supporting the treatment plan for restarting therapy after ICI-related colitis. A retrospective single-center study showed that there was no significant improvement in clinical outcomes and survival rates in patients who received rechallenging with ICIs after the occurrence of irAEs compared to those who discontinued ICI treatment.[22] The decision to restart ICI should be individualized and tailored to the patient's specific situation and response to initial therapy, and should follow relevant guidelines.

Conclusion

Colitis related to ICIs remains a significant concern in lung cancer patients and requires close monitoring and timely intervention. Restarting treatment after symptom relief can provide additional benefits for patients.

Ethics Approval Statement

This study was conducted with approval from the Ethics Committee of Peking Union Medical College Hospital. This study was conducted in accordance with the declaration of Helsinki. Since this study was a retrospective study and did not cause harm to patients, informed consent was waived.

Although patient consent to review medical records was waived by the Ethics Committee of Peking Union Medical College Hospital, all patient data was anonymized and handled with strict confidentiality in accordance with institutional guidelines and relevant regulations. Personal identifiers were removed to protect the privacy of the patients, and no identifying information was used in the analysis or publication of the data.

This statement ensures that ethical handling of patient information is emphasized while aligning with the decision of the Ethics Committee.

Disclosure

The authors report no conflicts of interest in this work.

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