Review Article

Management of immune check-point inhibitor-associated colitis in patients with advanced metastatic cancers: A review article

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Abstract

Immune check-point inhibitors (ICPi) are immunomodulating agents, which have revolutionized the management of advanced metastatic cancers. Being immunomodulating agents, they are predisposed to causing colitis. This descriptive review article emphasized on the management of ICPi-associated colitis in advanced metastatic cancers. We used PubMed, Google Scholar, Scopus, and Embase databases for literature review, and terminologies commonly searched were "management," "immune check-point inhibitors," "colitis," "metastatic," "cancers," "literature," and "review." We reviewed a total of 11 articles done in the last 15 years relevant to ICPi colitis and its management; all the articles showed that diarrhea and colitis are the most common adverse effects observed in patients on ICPi, but prior to establishing the diagnosis of ICPi-causing colitis, possibility of *Clostridium difficile* or cytomegalovirus infections should be ruled out. Once the diagnosis of ICPi colitis is established, treatment should be started depending upon the severity of colitis. In mild severity, discontinuation of ICPi can resolve the symptoms but, in most of the patients with moderate to high severity of colitis, corticosteroids are considered a cornerstone treatment. Patients unresponsive to steroid treatment should be re-evaluated for infections after which anti-TNF therapy—infliximab or vedolizumab, cyclosporine, mycophenolate mofetil—can be considered.

Keywords: Check point inhibitor, colitis, immune, management, metastatic cancer

Introduction

Immune check-point inhibitors (ICPi) have changed the landscape of different advanced metastatic cancers in the last several decades. They act by blocking either PD-L1 or CTLA-4, hindering the T-cell inactivation leading to increase in antitumor T-cell response. ICPi are considered as a treatment for advanced metastatic cancers including advanced non-small cell lung cancer (NSCLC), metastatic melanoma, endometrial cancer, or ovarian cancers. ICPi are immunomodulating agents stimulating immunity to fight the cancer, hence can cause inflammation of various organs of the body including liver and colon, causing colitis and hepatitis. Diarrhea and colitis are the most common adverse manifestations of ICPi due to which the treatment of ICPi-associated colitis has advanced in the last couple of decades. Here, we present a descriptive literature review on the treatment of ICPi-associated colitis in patients with advanced metastatic cancers. This study is

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relevant to the journal as ICPi-associated colitis is one of the most common presentations which get addressed by the primary care physicians and hospital medicine physicians.

Objectives

- The objectives of this study were as follows:
- To elaborate the management of ICPi-associated colitis
- To define the grading of colitis based on severity
- To elucidate the role of corticosteroids in the management of ICPi colitis
- To indicate the role of anti-TNF therapy including infliximab or adalimumab in corticosteroid refractory patients with advanced metastatic cancers
- - To clarify the importance of vedolizumab, cyclosporine, or mycophenolate mofetil in patients refractory to corticosteroids or anti-TNF therapy
- To put some light on considering early anti-TNF therapy in corticosteroid-unresponsive group in the first 48–72 hours

Methods and Methodology

Literature was reviewed on PubMed, Google Scholar, Embase, and Scopus databases and the keywords searched were "management," "immune check-point inhibitors," "colitis," "metastatic," "cancers," "literature," and "review." An extensive literature search for the last 15 years starting from 2006 till date was included in our study; most of the data studied was on ICPi-associated colitis in patients with advanced metastatic cancers. Adults of age >35 years, irrespective of the histology of cancer, were included in the study. Information was gathered from 11 most relevant articles and was arranged in descending order of the year of publication.

Literature Review

Zhang *et al*. (2021)

This was a retrospective study conducted at a single oncology center from March 2018 till May 2020 that included 11 patients, who failed both corticosteroids and infliximab treatment for ICPi colitis. Median age of patients included in the study was 53 years. Median onset of ICPi colitis was noted to be 4.43 weeks since the initiation of ICPi. Median time reported from onset of symptoms of colitis to commencement of calcineurin inhibitors including cyclosporine and tacrolimus was 70 days. Out of 11 patients, 8 responded well to calcineurin inhibitors, which was evident with improvement in clinical symptoms and endoscopic findings on all the patients included in the study. As a pre-requisite, all the patients were screened for hepatitis B, hepatitis C, varicella zoster, Epstein–Barr virus, and cytomegalovirus infections. Overall, calcineurin inhibitors were well tolerated, hence it was concluded that in patients with refractoriness to corticosteroids and infliximab treatment, calcineurin inhibitor treatment should be considered and, with close monitoring, adverse effects caused by calcineurin inhibitors including acute kidney injury can be addressed or avoided promptly.[1]

Durrechou *et al*. (2020)

This study emphasized the importance of ICPi toxicities and their management. ICPi have revolutionized the treatment of various cancers including NSCLC, ovarian cancers, and metastatic melanoma. Since the development of ICPi, progression-free span and overall survival rate have improved drastically by many folds. ICPi work by hindering immune effector inhibition, ultimately expanding pre-existing anticancer immune response. Considering that it is an immunomodulating drug, it does come with adverse effects including colitis. Patients with ICPi-associated colitis present with diarrhea, abdominal pain, rectal bleeding, weight loss, fever, vomiting, and oral or anal ulceration. Unfortunately, there are no specific markers to determine that the patients may have colitis in the future; hence, in this patient population, the patient is educated about the risk of changes in bowel transit times to avoid the development of grade 3–4 diarrhea secondary to colitis, thus preventing intestinal perforation which can ultimately lead to peritonitis. In patients with ICPi-induced colitis, always rule out *Clostridium difficle* infection and diverticulitis before jumping to the diagnosis of ICPi-causing colitis. Treatment of ICPi-causing colitis depends upon the intensity of symptoms. Infliximab can be considered in earlier stages of ICPi-induced colitis[2] but in patients with severe grade 3–4 colitis, other immunosuppressive agents including mycophenolate mofetil 500 to 1000 mg twice a day can be considered. The use of interleukin-17 inhibitor, vedolizumab, in the treatment of ICPi-induced colitis was currently under investigation for the treatment of ICPi causing colitis.[3] Role of budesonide as a prophylaxis was also considered with no significant improvement.[4]

Riveiro-Barciela *et al*. (2020)

Immunotherapy has become an adjuvant treatment in patients having metastatic cancers. Overall, all the patients on ICPi did develop adverse effects but when compared with platinum-based chemotherapy, grade 3 adverse effects were reported in only 10% of the population. Gastrointestinal symptoms were most reported with ICPi, with highest risk in first six months of initiation of immunotherapy. Diarrhea was the most common adverse effect reported in patients on ICPi especially in population on anti-CTLA-4 inhibitors as compared to PD-L1 inhibitors due to unidentified reasons. 27-54% patients receiving anti-CTLA-4 inhibitors developed diarrhea and 22% of patients developed colitis when compared with anti PD-L1 inhibitors.[5] Patients on ICPi if develop diarrhea should get a stool culture, Clostridium difficle serology, CT abdomen with contrast and endoscopic biopsy to rule out CMV colitis or metastasis.[6] In 97% of the cases, colitis was limited to rectum and sigmoid colon hence flexible sigmoidoscopy was diagnostic in most of the patients. Management of ICPi induced colitis depends upon the grading confirmed on scoping the patient. For grade 1 colitis, management is conservative including electrolyte repletion and loperamide as an anti-diarrheal agent, data on other anti-diarrheal agents is still uncertain and needs to be studied in ICPi colitis. Patient developing grade 2 colitis with systemic symptoms or grade 3 colitis were treated with corticosteroids with ICPi

withdrawal. If patient didn't improve clinically, single infusion of infliximab at a dose of 5 mg/kg can be considered to which patient usually responds but if patient doesn't respond to the treatment, repeat endoscopy was recommended to rule out CMV colitis before repeating infliximab dosage, as initial CMV testing can be falsely negative and considering anti-TNF alpha agents can disseminate the CMV infection which can be fatal. Another important issue discussed in the study includes the role of ICPi in patients having pre-existing IBD and it was concluded that pre-existing IBD should not be considered as a contraindication for using ICPi in management of advanced stage IV cancers.[7]

Som *et al*. (2019)

Som *et al*. conducted a study back in 2019 on management of adverse effects caused with ICPi. They elaborated that ICPi colitis can be categorized into four grades. Grade 1 defined as less than 4 stools per day, patient being diagnosed with grade 1 ICPi colitis can resume ICPi with electrolyte repletion and anti-diarrheal medication with loperamide, data on other anti-diarrheal still need to be studied. According to Som *et al*.,[8] grade 2 colitis can be labelled if patient is having 4 to 6 stools per day above their baseline bowel movements associated with abdominal pain, or blood and mucosa in the stool. In patient being diagnosed with grade 2 colitis, ICPi should be withheld temporarily, and patient must be started on oral corticosteroids at 0.5 to 1 mg/kg per day and consider one to two month tapered dose if symptoms persist for more than a week. For patient with grade 3 or 4 colitis, they must be having 7 or more stools above the baseline in a day, or presence of peritoneal signs with an ileus and fever which could be considered significant for bowel perforation. In this category, ICPi should be stopped permanently. All patients with above mentioned features should be hospitalized for intravenous fluid resuscitation. These patients must be started on high dose corticosteroids at a rate of 1-2 mg/kg per day only once clostridium difficle and ileus or perforation has been ruled out. Another study elaborated the role of infliximab in steroid refractory colitis patient. It was emphasized that patient if unresponsive to high dose steroids for 3 to 5 days should be considered with anti-TNF alpha therapy which did show excellent response once started earlier in the course of the disease.[9] It was summarized that early recognition and optimal management played the significant role in the treatment of ICPi colitis.[8]

Hamzah Abu-Sbeih *et al*. (2019)

This was a retrospective study conducted at MD Anderson Cancer Center, Houston, Texas in between January till December 2018 to emphasize on the importance of selective immunosuppressive therapy. Out of a total of 1459 patients receiving ICPi, 179 developed ICPi colitis. 84 out of the total of 179 patients received selective Immunosuppressive therapy (SIT) including infliximab or vedolizumab. Median time required for initiation of SIT was 10 days. Patient with early initiation of SIT required fewer hospitalizations, also had shorter duration of symptoms and less chance of failure of steroid taper respectively. Out of a total of 84 patients receiving SIT, 50 patients received infliximab and 34 patients received vedolizumab. Among infliximab group, only 4 patients were considered for vedolizumab infusion after infliximab treatment due to recurrence of the disease, out of which 3 still ended up having recurrence of the disease while 46 patients were just considered for early sole infliximab therapy, out of which only 12 patients developed recurrence. While on the other hand, in vedolizumab group, 2 patients were considered for infliximab infusion after receiving 3 infusions of vedolizumab out of which one patient did develop recurrence despite receiving both infliximab and vedolizumab therapy while remaining 32 patients just received early vedolizumab out of which only 1 patient developed recurrence which showed results in favor of early selective immunosuppressive therapy. It was concluded that selective immunosuppressive therapy should be initiated early after diagnosis of ICPi colitis, and it should not be held until steroid failure is evident to see drastic results of early immunosuppressive therapy in treatment of ICPi.[10]

Bajwa *et al*. (2019)

It was a systemic review including 139 case reports describing the adverse effects of ICPi in patients with metastatic cancers in between January 2016 till April 2018. ICPi have revolutionized the treatment of various cancers, which were considered as an untreated cancers couple of decades ago. ICPi works by excessive immune system activation against the cancer cells, hence ICPi are known for some immune mediated adverse effects including Colitis. 14 out of a total of 139 patients developed Colitis with ICPi. 3 developed ICPi after receiving pembrolizumab while 11 patients developed colitis after receiving nivolumab. On average, onset of colitis was more observed in patients after 13 doses of ICPi. Patients developing colitis were not dosage related as couple of patients did develop colitis after their first dose of ICPi. Patients developing ICPi colitis were treated with discontinuation of the inciting agent followed by starting the patients on prednisone to which if patient didn't respond well in 3 to 5 days were switched to anti TNF- alpha therapy including infliximab. It was concluded that, colitis is a common but manageable adverse effect of ICPi as all the patients developing colitis from ICPi in this study had complete resolution of symptoms with the treatment.[11]

Abu-Sbeih *et al*. (2018)

It was a retrospective descriptive multicenter study conducted at MD Anderson Cancer Center and Medstar Georgetown University center to determine the role of vedolizumab, a monoclonal antibody against integrins causing immunosuppression hence suppressing colitis caused by ICPi. This study included all the patients developing ICPi colitis refractory to steroids in between December 2016 and April 2018. Patient considered for refractoriness to steroids does include those with partial improvement in symptoms despite being on highest dose of corticosteroid therapy (2 mg/kg), symptoms relapse during tapering of corticosteroids or patient having signs and symptoms of dependency while being on steroids. Total of 28 patients were enrolled in the study who were given Vedolizumab. Mean

age on administration of Vedolizumab was 63 years. All the patients did fail corticosteroids therapy for a total of 96 days, 9 of the 28 patients did receive infliximab infusion with no significant response. After failing both corticosteroids and infliximab, vedolizumab at a standard dosing of 300 mg for each infusion was considered and patients were followed up for a total of 15 months since first infusion of vedolizumab. Median duration to improvement of symptoms was 5 days. Out of a total of 28 patients, 24 patients had sustained clinical remission, while 13 patients had endoscopic remission as well. Four patients did fail vedolizumab therapy most likely due to recurrent lymphocytic colitis. Clinical remission was attained in only 67% of the included subjects receiving infliximab before administration of vedolizumab as compared to 95% observed in patient population who didn't received infliximab therapy prior to vedolizumab. In conclusion it was reported that vedolizumab is highly effective in the treatment of ICPi induced colitis as compared to corticosteroids and infliximab but due to cost-effective, patients developing ICPi colitis should be considered for a trial of corticosteroids and infliximab before considering the candidacy for vedolizumab respectively.[12]

Collins *et al*. (2017)

It's a retrospective study conducted in between 2013 to 2016, Patient data was gathered from the pharmacovigilance registry. 44 patients with suspicion of colitis secondary to nivolumab or pembrolizumab were included in the study, among which eight developed colitis while 7 patients developed microscopic colitis. All the patients developing colitis were either having watery diarrhea or bloody diarrhea as a presentation. Colonoscopy did show acute mucosal ulceration with neutrophils and cryptitis in all patients with occasional mucosal infiltration with lymphocytes, plasma cells as well as crypt branching, and atrophy in patients having active colitis while colonoscopy on patients having microscopic colitis were macroscopically unremarkable. All the patients developing active colitis were treated with systemic corticosteroids, 87.5% achieved complete remission with systemic steroids, one patient failed the treatment hence received infliximab followed by vedolizumab, but patient had progression of the disease ultimately leading to death of the patient in 3 months. Patients developing microscopic colitis were initially treated with budesonide to which 67% of patients responded, rest were started on systemic corticosteroids followed by infliximab to which 33% of patient population developing microscopic colitis didn't responded well. In all the patients developing ICPi, check point inhibitors were held during the time when patient were having flare of colitis.[13]

Genova *et al*. (2017)

With the latest development in the management of advanced NSCLC, ICPi can be considered as a sole treatment in the patients having elevated PD-L1 levels. Gastrointestinal toxicities observed with ICPi mostly includes diarrhea or colitis, both can be a part of same clinical spectrum. Colitis caused by ICPi is further graded in to four different categories based on its severity. Grade 1 colitis is usually managed with loperamide started at 4 mg with first loose stool followed by 2 mg with every subsequent stool. Also, diarrhea associated with colitis might be controlled or treated with life-style modifications including small and frequent meals, hydro-saline and vitamin integration and limiting food including fruits, vegetables, caffeine, or alcohol which can exacerbate the condition. If the diarrhea persists despite treatment for 3 or more days, infection should be ruled out after which corticosteroids can be considered for the treatment of ICPi colitis in patients having advanced NSCLC. Most used corticosteroids include budesonide for the treatment of grade 2 to 4 colitis. If the patient failed corticosteroids, patients can be considered for infliximab or mycophenolate mofetil therapy. Despite being a potent-corticosteroids, budesonide isn't recommended to be given as a prophylaxis in the prevention of diarrhea or colitis being caused with ICPi. Patients with refractory colitis or if having red flag symptoms including advanced age, anemia or weight loss should be hospitalized for aggressive symptomatic relief being followed by corticosteroid treatment.[14]

Spain *et al*. (2016)

ICPi have changed the landscape of different metastatic cancers in last several years. These agents increase the anti-tumor T-cell response by blocking the interaction of PD1 and PD-L1, blocking T cell inactivation.[15] Considering that patients on ICPIs have an impaired T-cell inhibition, patients are at higher risk to develop adverse effects including colitis. Patients developing colitis as an adverse effect usually presents with diarrhea, lower abdominal pain, and rectal bleeding. Onset of colitis in patients on nivolumab is 7 weeks while patients on pembrolizumab can develop colitis in around 6 months.[16,17] Computed Tomography (CT) Scan findings of ICPi induced colitis includes mesenteric engorgement and bowel wall thickening.[18] Colitis caused by check-point inhibitors can be categorized in four sub-groups based of severity. Grade 1 colitis presents with less than 4 bowel movement a day which is treated with supportive care including fluids with loperamide. Grade 2 Colitis means having 4-6 bowel movements, treated with temporary holding off ICPIs, if no response in 5 days, patient should be started on prednisolone at a rate of 0.5 to 1 mg/kg, and if no response in 2-4 weeks consider managing the patient as having grade 3 colitis in which patients starts to have 7 or more bowel movements which is treated with supportive care with admission to the hospital including intravenous hydration, clinical observation and starting the patients on prednisolone at the rate of 1-2 mg/kg. if no improvement in 2-3 days, infliximab at a rate of 5 mg/kg can be considered. Infliximab is contraindicated in patients having sepsis or GI perforation. Once patient colitis starts to show improvement and decreased to grade 1, patient can be started on steroid taper for 1-3 months but if non-responsive consider re-administration of infliximab at 2 and 6 weeks. Grade 4 colitis is life threatening for which emergent surgical or gastroenterology consultation should be considered along with permanent discontinuation of ICPIs.[19]

Friedman *et al*. (2016)

ICPi are the ground-breaking development in treatment of NSCLC. Two specific targets evaluated in detail includes programmed cell death (PD-1) or Cytotoxic T-lymphocyte Antigen (CTLA-4) respectively. ICPi impairs the immunologic homeostasis by blocking the negative regulators of immunity hence causing adverse effects including colitis. In general, agents that block PD-1 have fewer adverse effects (1.8%) as compared to CTLA inhibitors (7%) due to unidentified reasons. Patients on ICPI usually develops diarrhea or colitis in 6 to 8 weeks of initiation of therapy. Patient being on ICPi when presents with diarrhea, initial step is always to rule out infectious cause including Clostridium difficle infection. In patients with mild inflammation causing diarrhea, patients are usually treated with supportive care and loperamide. If symptoms persist despite being treated with supportive care and imaging is evident for colonic inflammation patient should be considered for oral prednisone 1-2 mg/kg daily or IV methylprednisolone up to 2 mg/kg twice daily. If the colonic inflammation is severe, patients usually get hospitalized for supportive care and IV steroids which if patient is refractory, are switched to infliximab. Patient developing colitis with one ICPi agent doesn't prohibit the treatment with another member of the drug category. Also, whenever we have grade II or severe colitis, treatment with ICPi was held every time till colitis stage improved down to stage 1 or resolved.[20]

Discussion

Immune Check-Point Inhibitors (ICPi) have revolutionized the treatment of various cancers including Non-small cell Lung cancer (NSCLC), ovarian cancer, endometrial cancers, and metastatic melanoma. It's an immunomodulating agent which improves the immunity against cancer cells by increasing the T cell response by blocking the interaction of PD1 and PD-L1 ultimately inhibiting T-Cell inhibition. Considering that, it stimulates or improves the immunity to fight the cancer cells, it does come with adverse effects including colitis.

In patients with diarrhea after administration of ICPi, colonic infections including clostridium difficle should be ruled out after which diagnosis of ICPi causing colitis can be established. Management should be started depending on the burden of symptoms. Symptom severity is graded by number of daily bowel movements and complications: Grade 1 colitis is considered when patient is having less than 4 bowel movements a day, grade 2 colitis is considered when bowel movements are 4-6 in a day, grade 3 is considered when patients are having more than 7 bowel movements in a day and grade 4 is considered when life threatening consequences including perforation or intestinal obstruction get diagnosed in these patients, emergent general surgery consultation is warranted (CTCAE v 5.0).[21]

Grade 1 colitis is easily treated with conservative measures including loperamide, repleting electrolytes and hydration; in most of the cases with grade 1 ICPi causing colitis, ICPi can be continued.[7,8] In contrast, Grade 2 colitis responds well to temporary cessation of ICPi, and corticosteroids should be trialed.[19] Grade 3 and 4 colitis often also respond well to corticosteroids; however, ICPi therapy should be permanently discontinued.[7,8,19] Hospitalization where IV rehydration and immunotherapy can be carefully provided should be considered for patients with grade 3 or 4 colitis.[8]

Several studies have shown benefit from early immunosuppressive therapy; however, one study suggested waiting several days after cessation of the ICPi to identify if colitis would resolve without therapy.[19] Oral or IV steroids can initially be started at 0.5-1.0 mg/kg; oral steroids may not be absorbed as well in patients with frequent diarrhea. An initial steroid trial may vary in duration from 3-7 days.[8,13]

Steroid therapy alone has been found to be very effective. Collins *et al.* found corticosteroids can result in complete remission nearly 87.5% of the time. If corticosteroids are not effective, possibility of clostridium difficle and cytomegalovirus infections should be ruled out before stepping up the treatment regimen.[4,7] When diarrhea persists despite therapy, direct visualization of the colon with flexible sigmoidoscopy is useful to evaluate for infection, differentiate microscopic colitis, and obtain histologic confirmation of ICPi colitis.

If there is no evidence of infection, symptoms may truly represent refractory disease. Corticosteroid therapy may be first up titrated to methylprednisolone 2 mg/kg twice daily.[12,20] Depending on response, corticosteroids may be continued for longer duration of time.[8] Additional benefit may be gained by adding TNF-alpha therapy such as infliximab to corticosteroid therapy.[12] Infliximab is commonly utilized next for continued symptoms due to efficacy and cost-effectiveness.[7,8,14] Vedolizumab is superior to infliximab; however, this therapy is prescribed less frequently as it's less cost effective when compared with corticosteroids or infliximab.[10] Other medications like calcineurin inhibitors and mycophenolate mofetil have been shown to be effective after an infliximab-trial but the studies are limited in this regard.[1]

Additional studies are needed to identify rates of ICPi colitis recurrence after ICPi therapy is adjusted particularly for Grade 2 and 3 colitis. Both PD-1 inhibitors and CTLA-4 inhibitors are known to cause ICPi; however, PD-1 inhibitors have been noted to cause less adverse effects. Data regarding transitioning from CTLA-4 inhibitor therapy to PD-1 inhibitors are lacking.[20] Another aspect which requires further discernment is prophylaxis. Budesonide has not been shown helpful for prophylaxis; however, if efficacious prophylaxis can be provided, therapy will be better tolerated.[4,14] Lastly, if patients at high risk of developing ICPi-colitis can be identified, ICPi therapy may be more carefully considered, and the side-effects more readily anticipated.

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Conflicts of interest

There are no conflicts of interest.

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