

## Ipilimumab Induced Enterocolitis: A Fatal Immune-Related Adverse Event of Melanoma Treatment

Chandamuri Babi, Spiegel Jaclyn, Nicaud Mark, Hutchings John

Chandamuri Babi, Spiegel Jaclyn, Nicaud Mark, Hutchings John, Department of Internal Medicine and Department of Gastroenterology, LSU-Health Sciences Center, New Orleans, LA, the United States

Correspondence to: Chandamuri Babi, Department of Internal Medicine and Department of Gastroenterology, LSU-Health Sciences Center, New Orleans, LA, the United States.

Email: [bchan1@lsuhsc.edu](mailto:bchan1@lsuhsc.edu)

Received: September 4, 2013

Revised: November 2, 2013

Accepted: November 9, 2013

Published online: December 21, 2013

### ABSTRACT

Ipilimumab is a human monoclonal antibody that has recently been approved for treatment of stage III or IV melanoma. Although it is has proven to be a generally safe drug, treatment with ipilimumab has been associated with potentially fatal adverse effects. We present a fatal case of enterocolitis caused by just one cycle of ipilimumab therapy.

© 2013 ACT. All rights reserved.

**Key words:** Ipilimumab, Diarrhea, Enterocolitis, Melanoma, Immune, Adverse

Babi C, Jaclyn S, Mark N, John H. Ipilimumab Induced Enterocolitis: A Fatal Immune-Related Adverse Event of Melanoma Treatment. *Journal of Gastroenterology and Hepatology Research* 2013; 2(12): 934-936 Available from: <http://www.ghrnet.org/index.php/joghr/article/view/552>

### INTRODUCTION

Ipilimumab (trade: Yervoy) is a full human monoclonal antibody directed against cytotoxic T-lymphocyte antigen-4 (CTLA-4), a prominent negative regulator in T cell activation. Ipilimumab was approved by the Food and Drug Administration in March of 2011 for unresectable stage III or IV melanoma. Recent phase III trials have shown a statistically significant survival benefit in previously treated patients with advanced melanoma. Although ipilimumab

has a manageable safety profile, treatment has been associated with potentially fatal adverse effects, most notable immune-related Adverse Events (irAEs). Most of the reported serious complications of ipilimumab treatment are associated with the gastrointestinal (GI) tract; including diarrhea, abdominal pain, and bloating<sup>[1]</sup>. Here, we present an unfortunate case of fatal colitis caused by one cycle of ipilimumab infusion.

### CASE REPORT

A 63 year-old female with no previous medical history was seen for her routine gynecology clinic visit, at which time, she complained of bright red blood on her toilet tissue. On exam, an anal mass of approximately 2×4 cm was discovered. Additionally, multiple condylomas on her labia majora were found. The patient was sent to general surgery for biopsy. Pathology of the biopsy specimen revealed malignant melanoma with superficial ulceration. Four other lesions around her anus were biopsied and proved to be human papillomavirus-positive condylomas. Pathological stains revealed that the tissue from the primary anal was strongly positive for melanA and S-100. The patient was seen by oncology and CT scans of the chest and abdomen revealed multiple bilateral pulmonary nodules, a 1.3×0.9 cm ring-enhancing lesion in the liver, a lucent area within the T6 vertebral body with surrounding osteolytic areas, and periperitoneal nodules, all suspicious for metastatic disease. Thus, her disease was deemed to be stage IV, T3NXM1. Other than the BRBPR, the patient was asymptomatic and hemoglobin was within normal range.

Her tumor was BRAF mutation negative, thereby, she was not a candidate for vemurafenib therapy and ipilimumab treatment was chosen. Initial plan for her treatment included four cycles of ipilimumab infusion every three weeks. She was also started on zoledronic acid for her spinal lesion.

She tolerated the induction ipilimumab infusion, but one week later, she reported general malaise and intractable voluminous, non-bloody, diarrhea – occurring six to eight times per day- that prevented her from going to work. She was found to have grade II reaction to ipilimumab and was started on 0.5 mg/kg/day of oral prednisone until symptom resolution.

One week later (two weeks after ipilimumab induction), she presented to the Emergency Room with severe worsening diarrhea,

unchanged in nature, not relieved with loperamide – now occurring more than ten times daily. She was admitted to the hospital with chemotherapy-related colitis and mucositis and she was placed on broad-spectrum antibiotic coverage and given IV hydration. CT scan revealed severe pan-colitis, and her second cycle of chemotherapy was held. Stool studies were negative for *C. Difficile* as well as ova, parasites, and leukocytes. After 3 days, her bowel movements became sanguinous. At that point oral prednisone was escalated to intravenous solumedrol. After 3 days on IV steroids, her diarrhea improved slightly and bowel movements returned to non-bloody in nature. IV steroids were de-escalated to PO prednisone, but after 2 days of PO conversion, she had recurrent bloody bowel movements. Following a general surgery consult, palliative resection of her anal mass was deemed not to be possible. The patient was also evaluated by gastroenterology for lower endoscopy, but this was deferred due to concern for colonic perforation. Massive blood loss from her colitis and friable anal lesion became so great that she required a transfusion and initiation of IV iron supplementation. The patient became dependent on scheduled antidiarrheals for any symptom relief, and further attempt to convert her back to oral steroids failed.

Radiation oncology was consulted, who began treatment of her anal and spinal lesions. Due to blood loss and intense electrolyte derangement, care was deemed to be futile. However, ten treatments of palliative radiation were planned too attempt to relieve her severe pain, but the patient's bilateral lower extremity weakness increased to the degree that she could no longer walk and she was having increasingly severe bladder retention, at which time a follow-up CT scan revealed that her T6 spinal lesion was compressing her spinal cord. Neurology was recommended to change her intravenous solumedrol to intravenous decadron in an effort to alleviate some of the spinal compression. The patient's pain and weakness progressed to the point where she became dependent on a morphine infusion for pain relief, and the patient expired on hospital day 37.

## DISCUSSION

This case illustrates an example of one of the most serious adverse effects of ipilimumab therapy: enterocolitis-induced diarrhea. The development of severe diarrhea (an increase of at least 6 diarrhea bowel movements from baseline) can be expected after multiple treatments with Ipilimumab. The incidence of diarrhea in patients receiving ipilimumab treatment has been reported to be anywhere from 18 to 44 percent<sup>[2]</sup>. In some cases, the colitis has led to obstruction and perforation. Though mortality in patients who developed colitis is reported to be up to 5%, fatal complications of colitis rarely occur after only a single dose of Ipilimumab. Our case is unique in that our patient unfortunately developed severe diarrhea after only one dose of Ipilimumab. Furthermore, the complications of blood loss and electrolyte derangement ultimately were her the cause of death.

irAE related colitis most often affects the descending colon and histologically is most frequently associated with a neutrophilic infiltrate though lymphocytic and mixed infiltrates have been reported as well. Wang *et al.* show that blockade of the CTLA-4 by ipilimumab results in GI irAEs. They describe that fluctuating antibody titers to enteric flora, which are a hallmark of inflammatory bowel disease, but not acute GI inflammation such as infection or diverticulitis, resulted from interruption in GI mucosal immunity from CTLA-4 blockade by ipilimumab. They also showed that CTLA-4 pathway blockade resulted in increased levels of neutrophil-derived fecal calprotectin (a biomarker of bowel inflammation), and mucosal immune infiltration<sup>[3]</sup>. The fluctuation of antibody titers

to intestinal flora is also a feature of graft-versus-host disease, a similarity noted by Beck *et al.*<sup>[4]</sup>.

Wang *et al* were able to gather data from colonic biopsies in patients thought to have ipilimumab-induced diarrhea. They show that these biopsies differ from those of patients with Ulcerative Colitis with regards to chronicity and lack of involvement of the distal colon. Though our patient did not have a colonoscopy, imaging revealed diffuse colitis involving the descending colon. Regarding endoscopic evaluation of the ipilimumab-induced diarrhea group, Wang *et al* also describe the lack of unique features of Crohn's disease such as aphthous ulcers, granulomas, or transmural inflammation<sup>[3]</sup>. However, Beck *et al.* show that there are similarities in the colitis after ipilimumab to that of inflammatory bowel disease such as pictures of acute and chronic inflammation, skip areas, and response to infliximab<sup>[4]</sup>.

The mainstay of treatment is primarily a short course of glucocorticoids until symptom resolve as well as delaying or ceasing further ipilimumab therapy. If the diarrhea is limited to two loose bowel movements per day, then therapy can be supportive with hydration and electrolyte replacement and antidiarrheals such as loperamide. If the diarrhea is more severe and infectious sources have been ruled out, oral steroids should be used. Some authors recommend lower endoscopy in cases of persistent diarrhea or rectal bleeding to rule out colitis. However, the risk of perforation has been reported to be as high as 20%<sup>[5]</sup>. If symptoms do not resolve with oral steroids or loose bowel movements increase to seven per day, intravenous steroids should be used along with aggressive hydration. Usually, intravenous (IV) steroids lead to symptom improvement, however a long 6 to 8 week steroid taper should be used to avoid recurrence. Our patient responded fairly well to IV steroids, however, once we attempted to convert her regimen to oral steroids, not only did her diarrhea worsen, she began to experience bright red blood per rectum, though it should be noted this may have been due to oozing from her rectal mass. It is unclear if this oozing was caused by steroid reduction.

For patients who do not respond to IV steroids in 72 hours, treatment with infliximab can be considered. Reports of rapid response to infliximab have been reported. Once response is observed, infliximab should be stopped and protracted steroid taper of 6-8 weeks should be implemented. Infliximab is thought to be effective because it opposes activation of T cells by CTLA-4 antibodies.

Revicki *et al* tested budesonide as prophylaxis of diarrhea and colitis in patients undergoing ipilimumab treatment without any noticeable difference with the placebo group<sup>[6]</sup>. Accordingly, prophylactic use of oral steroids to prevent diarrhea is not recommended.

Enterocolitis induced diarrhea is perhaps the most common adverse effect of ipilimumab therapy. Although the incidence of this effect has been reported to be as low as 18% and there have been many successfully treated cases, here we present the unfortunate case of a fatal case of ipilimumab induced enterocolitis - after a single dose of Ipilimumab therapy. Even with steroid treatment, our patient was not able to tolerate effects of therapy. Though ipilimumab has proven to be successful in the treatment of stage III and IV melanoma, complete risks and benefits of therapy should be weighed prior to induction, especially in cases where the patient has a good functional status at time of cancer diagnosis.

## REFERENCES

- 1 Camacho LH, Antonia S, Sosman J, Kirkwood JM, Gajewski TF, Redman B, Pavlov D, Bulanhagui C, Bozon VA, Gomez-

- Navarro J, Ribas A. Phase I/II trial of tremelimumab in patients with metastatic melanoma. *J Clin Oncol* 2009; **27**: 1075-1081
- 2 Tsao H, Atkins MB, Sober AJ. Management of cutaneous melanoma. *N Engl J Med* 2004; **351**: 998-1012
  - 3 Wang T, Somasundaram R, Herlyn M. Combination therapy of immunocytokines with ipilimumab: a cure for melanoma? *J Invest Dermatol* 2013 Mar; **133**(3):595-596. doi: 10.1038/jid.2012.433.
  - 4 Beck KE, Blansfield JA, Tran KQ, Feldman AL, Hughes MS, Royal RE, Kammula US, Topalian SL, Sherry RM, Kleiner D, Quezado M, Lowy I, Yellin M, Rosenberg SA, Yang JC. Enterocolitis in patients with cancer after antibody blockade of cytotoxic T-lymphocyte-associated antigen 4. *J Clin Oncol* 2006 May 20; **24**(15): 2283-2289
  - 5 Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzalez R, Robert C, Schadendorf D, Hassel JC, Akerley W, van den Eertwegh AJ, Lutzky J, Lorigan P, Vaubel JM, Linette GP, Hogg D, Ottensmeier CH, Lebbé C, Peschel C, Quirt I, Clark JL, Wolchok JD, Weber JS, Tian J, Yellin MJ, Nichol GM, Hoos A, Urba WJ. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010; **363**: 711-723
  - 6 Revicki DA, van den Eertwegh AJ, Lorigan P, Lebbe C, Linette G, Ottensmeier CH, Safikhani S, Messina M, Hoos A, Wagner S, Kotapati S. Health related quality of life outcomes for unresectable stage III or IV melanoma patients receiving ipilimumab treatment. *Leuk Res* 2013 Mar; **37**(3): 259-265. doi: 10.1016/j.leukres.2012.11.017. Epub 2012 Dec 27.

**Peer reviewer:** Ian Lawrance Lawrance, Professor, School of Medicine and Pharmacology, Level 5, T Block, Alma Street, Fremantle Hospital, Fremantle, 6160, WA, AUSTRALIA.