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Risk of Bowel Perforation in Patients Receiving Interleukin-2 After Therapy With Anti-CTLA 4 Monoclonal Antibody

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To the Editor

The Surgery Branch at the National Cancer Institute has had extensive experience with the intravenous administration of high-dose inter-leukin-2 (IL-2) and anti-CTLA 4 antibody (MDX010, Ipilimumab) in patients with metastatic melanoma or metastatic renal cell cancer as standard cancer therapy or in clinical trials. The purpose of this letter is to report a possible increase in a rare IL-2 toxicity after therapy with anti-CTLA 4 antibody.

Twenty-two patients in the Surgery Branch received intravenous anti-CTLA 4 antibody while participating in experimental therapies and at some later point received treatment with high-dose IL-2 therapy at 720,000 U/kg every 8 hours. Retrospective analysis of our data showed that 3 of these 22 patients developed bowel perforations during their treatment with high-dose IL-2 and subsequently required emergency laparotomy (Table 1).

There did not seem to be a temporal relationship between the anti-CTLA 4 antibody administration and the dosing with IL-2. There was an average of 86 days between the last dose of anti-CTLA 4 antibody and the start of IL-2 therapy. All 3 patients were asymptomatic before starting IL-2 therapy.

Although the numbers are small, this incidence of 13.6% contrasts significantly with our experience with bowel perforations in patients treated with high-dose IL-2 alone of less than 1%. In a retrospective analysis done in the Surgery Branch of patients treated between November 1, 1998 and May 1, 2002 with IL-2 alone¹ there were 8 perforations out of 1797 patients (0.45%; $P_2 = 0.002$ compared with patients treated with anti-CTLA 4 antibody followed by IL-2). In 198 patients treated in the Surgery Branch with anti-CTLA 4 antibody alone between March 19, 2002 and July 15, 2005² there were 4 perforations (2%; $P_2 = 0.024$ compared with patients treated with anti-CTLA 4 followed by IL-2).

Two of the 3 patients who developed bowel perforation while receiving IL-2, had autoimmune colitis after treatment with anti-CTLA 4 antibody. The third patient had no symptoms of colitis. The pathology from all 3 patients demonstrated active chronic colonic colitis with intraepithelial lymphocytosis.

To reduce the risk of this complication it is our recommendation that patients who have received prior anti-CTLA 4 antibody, and who plan to receive treatment with IL-2 undergo diagnostic colonoscopy before initiating IL-2 to rule out chronic active colitis. This should be considered regardless of whether the patients have experienced colitis due to anti-CTLA 4 antibody or not.

In the Surgery Branch this has led to increased interest in further studying the immunologic and pathologic mechanisms of the colitis due to IL-2 and anti-CTLA 4 antibody.

References

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2. Beck KE, Blansfield JA, Tran KQ. Entero-colitis in patients with cancer after antibody blockade of CTLA 4 antibody. *J Clin Oncol* 2006;24:2284–2289.

TABLE 1
 Bowel Perforations in Patients Treated With IL-2 After Prior Therapy With Anti-CTLA 4 Antibody

Patient	Documented Autoimmune Colitis During Anti-CTLA 4 Antibody Therapy	Time (Days) Between Last Dose of Anti-CTLA 4 Antibody and IL-2	Outcome
1	Yes	101	Sigmoid resection and Hartmann's procedure
2	No	77	Left hemicolectomy and Hartmann's procedure
3	Yes	80	Extended left hemicolectomy and Hartmann's procedure