

HEMATOLOGY

Ipilimumab of benefit in unresectable melanoma

Ipilimumab is a monoclonal antibody against CTLA-4 that has shown encouraging results when used as treatment for advanced melanoma. Its use, however, is associated with immune-related adverse effects, including severe colitis and diarrhea. Weber and colleagues hypothesized that prophylactic treatment with the oral corticosteroid, budesonide (which has low systemic bioavailability owing to its extensive first-pass metabolism) could improve the gastrointestinal adverse effects associated with ipilimumab without comprising its antitumor activity.

“...budesonide does not impair the ... activity of ipilimumab [but] should not be used prophylactically...”

This phase II, randomized, double-blind, multicenter, placebo-controlled trial

included 115 patients with unresectable stage III or IV melanoma who were treated with ipilimumab and either budesonide ($n = 58$) or placebo ($n = 57$). The primary end point was the rate of grade 2 or above diarrhea during the first 24 weeks of treatment. The Common Terminology Criteria for Adverse Events were used to assess diarrhea. The first tumor assessment took place at week 12.

The rate of grade 2 or above diarrhea was similar in both treatment groups, and overall side-effects were comparable for those treated with budesonide or placebo. The median overall survival was 17.7 months for patients treated with budesonide and 19.3 months for those treated with placebo. The best overall response rate was 12.1% for patients treated with budesonide and 15.8% for patients in the placebo group. Patients with grade 3–4 immune-related adverse events achieved the highest rates of disease control in both groups.

The results of this trial confirm the efficacy of ipilimumab in patients with metastatic melanoma. Although budesonide does not impair the antitumor activity of ipilimumab it should not be used prophylactically for the prevention of ipilimumab-associated diarrhea. Jeffrey Weber added, “The most important findings of this study ironically do not relate to the primary end point of reduction of diarrhea and colitis, which did not occur, but to the very impressive and long median and 24-month survivals seen with the drug, especially in the previously untreated patients.”

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Original article Weber, J. *et al.* A randomized, double-blind, placebo-controlled, phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage III or IV melanoma. *Clin. Cancer Res.* **15**, 5591–5598 (2009).