Published OnlineFirst April 21, 2014; DOI: 10.1158/2326-6066.CIR-14-0053

Research Article

Cancer Immunology Research

Bevacizumab plus Ipilimumab in Patients with Metastatic Melanoma

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Abstract

Ipilimumab improves survival in advanced melanoma and can induce immune-mediated tumor vasculopathy. Besides promoting angiogenesis, vascular endothelial growth factor (VEGF) suppresses dendritic cell maturation and modulates lymphocyte endothelial trafficking. This study investigated the combination of CTLA4 blockade with ipilimumab and VEGF inhibition with bevacizumab. Patients with metastatic melanoma were treated in four dosing cohorts of ipilimumab (3 or 10 mg/kg) with four doses at 3-week intervals and then every 12 weeks, and bevacizumab (7.5 or 15 mg/kg) every 3 weeks. Forty-six patients were treated. Inflammatory events included giant cell arteritis ($n = 1$), hepatitis ($n = 2$), and uveitis ($n = 2$). On-treatment tumor biopsies revealed activated vessel endothelium with extensive $CD8^+$ and macrophage cell infiltration. Peripheral blood analyses demonstrated increases in $CCR7^{+/-}/CD45RO^+$ cells and anti-galectin antibodies. Best overall response included 8 partial responses, 22 instances of stable disease, and a disease-control rate of 67.4%. Median survival was 25.1 months. Bevacizumab influences changes in tumor vasculature and immune responses with ipilimumab administration. The combination of bevacizumab and ipilimumab can be safely administered and reveals VEGF-A blockade influences on inflammation, lymphocyte trafficking, and immune regulation. These findings provide a basis for further investigating the dual roles of angiogenic factors in blood vessel formation and immune regulation, as well as future combinations of antiangiogenesis agents and immune checkpoint blockade. *Cancer Immunol Res; 2(7); 632–42. ©2014 AACR.*

Introduction

CTLA4 blockade with ipilimumab improves survival in patients with metastatic melanoma when compared with a gp100 peptide vaccine (1) and in combination with dacarbazine chemotherapy when compared with dacarbazine alone (2). Efforts to further enhance the efficacy of immune checkpoint blockade through rational treatment combinations are needed.

In pursuit of predictive markers, pretreatment levels of vascular endothelial growth factor (VEGF-A) influence clinical outcomes to ipilimumab therapy (3). Therefore, determinants that may limit ipilimumab efficacy include immunosuppressive angiogenic factors such as VEGF. VEGF has profound effects on immune regulatory cell function, specifically inhibiting dendritic cell maturation and antigen presentation (4, 5). Furthermore, there is increasing evidence for the role angiogenic factors play in influencing lymphocyte trafficking across endothelia into tumor deposits (6). Previous studies have demonstrated the effects of ipilimumab on vessels feeding tumor deposits, resulting in an immune-mediated vasculopathy (7). As a result of CTLA4 blockade, granulocytes and lymphocytes infiltrate the endothelia, resulting in its destruction and tumor necrosis. The clinical efficacy of targeting VEGF-A and its effects on pathologic angiogenesis have been extensively studied with the use of bevacizumab (8–14), and these findings suggest a role in counteracting the immunosuppressive actions of VEGF. Given the effects on tumor vasculature witnessed in patients with melanoma being treated with ipilimumab and the known activity of bevacizumab, we conducted a phase I study to investigate the potential synergies of this combination in patients with metastatic melanoma.

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Note: Supplementary data for this article are available at Cancer Immunology Research Online (http://cancerimmunolres.aacrjournals.org/).

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doi: 10.1158/2326-6066.CIR-14-0053

Materials and Methods

Study design and treatment

The protocol (Supplementary Appendix A) was approved by the Dana-Farber/Harvard Cancer Center institutional review