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Short Report

Ipilimumab and Bevacizumab in Glioblastoma

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Abstract

The median survival in glioblastoma is just over a year, with no standard second-line therapy. Ipilimumab is an immune checkpoint inhibitor that activates the anti-tumour immune response by cytotoxic T-lymphocyte antigen-4 blockade. There is significant evidence supporting its role in the treatment of malignant melanoma, including in patients with brain metastases. The addition of the anti-angiogenesis agent, bevacizumab, seems to offer additional benefit and limit the immune-related side-effects of ipilimumab in melanoma. To date there have been no clinical trials investigating this combination in glioblastoma. In this single practice case series, 20 patients with glioblastoma were consented for and treated with ipilimumab and bevacizumab in combination. Safety, tolerability and the response to treatment were reviewed for all patients. Three patients were treated after palliative first-line radiotherapy, one patient after first-line chemoradiation and 16 patients were treated with recurrent disease. Sixty-five per cent of patients completed four cycles of 3 weekly ipilimumab therapy, administered with 2 weekly bevacizumab. Radiographic responses for patients with recurrent disease were evaluated by Response Assessment in Neuro-oncology (RANO) criteria; 31% of patients showed a partial response, 31% had stable disease and 38% had disease progression. The treatment combination was well tolerated, with treatment terminated before completion due to adverse events in two patients. Autoimmune toxicity was manageable with systemic corticosteroid therapy. Ipilimumab and bevacizumab in combination show promising activity with a predictable and manageable toxicity profile, warranting further clinical studies.

Key words: Bevacizumab; glioblastoma; high grade glioma; immunotherapy; ipilimumab

Introduction

Glioblastoma is the most commonly occurring primary brain tumour. It remains associated with a very poor prognosis and a median survival of just over a year [1]. First-line treatment is surgical resection followed by radiotherapy and temozolomide chemotherapy [2]. There is no standard second-line therapy and most patients either receive a lomustine-containing chemotherapy regimen or enter clinical trials.

Ipilimumab is a fully humanised IgG1 monoclonal antibody that potentiates the anti-tumour T-cell response by blocking the cytotoxic T-lymphocyte antigen-4, a critical negative regulator (checkpoint) of T-cells. To date, the majority of clinical experience and efficacy data for ipilimumab are in the setting of metastatic malignant melanoma [3], for which it has become an established treatment leading to durable long-term survival in a subset of patients with advanced disease [4]. Ipilimumab has also shown responses in patients with malignant melanoma and brain metastases [5], highlighting efficacy within the central nervous system.

Ipilimumab has been administered safely alongside bevacizumab in melanoma, with evidence of synergistic efficacy and manageable toxicity when compared with ipilimumab alone [6]. Bevacizumab is a humanised monoclonal antibody that targets vascular endothelial growth factor. Studies have shown bevacizumab to be well tolerated in both newly diagnosed and recurrent glioblastoma, with evidence of anti-tumour and anti-oedema activity [7]. Although the addition of bevacizumab to standard therapy in newly diagnosed glioblastoma shows no improvements

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in overall survival [8], there is some evidence that it can preserve quality of life and performance status [9]. To date, there have been no clinical trials investigating the combination of ipilimumab and bevacizumab in glioblastoma. We describe here the safety and tolerability of a treatment regimen containing ipilimumab and bevacizumab.

Patients and Methods

Twenty patients with glioblastoma who had previously received treatment with first-line therapy as tolerated were consented for treatment with an off-label regimen combining ipilimumab and bevacizumab; granulocyte-colony stimulating factor was included to boost peripheral white cell counts, reduce chemotherapy-induced myelosuppression and potentiate anti-tumour immunity [10]. Treatment was given either in place of or alongside oral palliative chemotherapy. Nineteen patients had confirmed World Health Organization grade IV disease and one patient had a recurrent astrocytoma (grade II), radiologically consistent with grade IV disease. Sixteen patients were treated after disease progression; two of these patients had completed first-line chemoradiotherapy within 3 months. Three of the remaining patients were treated after first-line short-course radiotherapy, and one was treated after standard chemoradiotherapy. All patients who began treatment with the regimen were included in the analysis. Patient demographics and biomarkers including methylguanine methyltransferase promoter methylation and isocitrate dehydrogenase-1 mutation status are shown in Table 1.

Ipilimumab was dosed at 3 mg/kg body weight every 3 weeks for four cycles followed by maintenance therapy every 12 weeks. Each ipilimumab dose was followed by granulocyte-colony stimulating factor within 24 h. Bevacizumab was dosed at 10 mg/kg, administered every 2 weeks. Patients were assessed before each treatment with a full clinical review and standard blood tests, including thyroid function. Interim 6 weekly magnetic resonance imaging scans were carried out to determine disease response. Adverse event data were recorded and analysed to determine safety and tolerability. Radiographic responses were assessed using the Response Assessment in Neuro-oncology (RANO) criteria [11].

Results

Between January 2014 and April 2015, 20 patients began treatment with four 3 weekly cycles of ipilimumab in addition to 2 weekly bevacizumab. Of these patients, 13 patients (65%) completed all four cycles. In the seven patients who did not complete four cycles, the reasons were dose-limiting toxicity (two patients) and clinical deterioration (five patients). Of the 13 patients who completed all four standard cycles, nine (69%) proceeded to maintenance therapy. All patients underwent interim magnetic resonance imaging 6 and 12 weeks after the start of treatment to determine the response to treatment, with responses

Table 1
Patient demographics, first-line treatment and biomarkers

Patient	Histological diagnosis	MGMT methylation status	IDH-1 mutation status	Gender	Age at treatment	First-line treatment received
First-line treatment						
1	Glioblastoma	10%	Negative	Female	54	Short-course radiotherapy
2	Glioblastoma	Methylated	Negative	Female	46	Short-course radiotherapy
3	Glioblastoma	Not available	Negative	Male	60	Short-course radiotherapy
4	Glioneuronal Tumour	Unmethylated	Negative	Male	23	Radiotherapy with TMZ
Recurrent disease						
5	Astrocytoma	10%	Negative	Female	31	Radiotherapy alone 7 cycles TMZ
6	Gliosarcoma	Unmethylated	Negative	Female	38	Chemoradiotherapy 5 cycles TMZ
7	Glioblastoma	Unmethylated	Negative	Female	48	Chemoradiotherapy 2 cycles TMZ
8	Glioblastoma	Methylated	Negative	Male	55	Chemoradiotherapy 6 cycles TMZ
9	Glioblastoma	10%	Negative	Male	45	Chemoradiotherapy 12 cycles TMZ
10	Glioblastoma	Unmethylated	Negative	Male	23	Chemoradiotherapy 6 cycles TMZ
11	Glioblastoma	Unmethylated	Negative	Male	35	Chemoradiotherapy 8 cycles TMZ
12	Glioblastoma	Unmethylated	Negative	Female	28	No radiotherapy
13	Glioblastoma	Unmethylated	Negative	Female	52	Chemoradiotherapy 4 cycles TMZ
14	Glioblastoma	5%	Negative	Male	58	Chemoradiotherapy 6 cycles TMZ
15	Glioblastoma	Unmethylated	Negative	Male	40	Chemoradiotherapy 0 cycles TMZ
16	Glioblastoma	10%	Negative	Male	69	Chemoradiotherapy 9 cycles TMZ
17	Glioblastoma	Not available	Not available	Male	66	Chemoradiotherapy 6 cycles TMZ
18	Glioblastoma	10%	Negative	Male	69	Chemoradiotherapy 7 cycles TMZ
19	Glioblastoma	Methylated	Negative	Female	46	Chemoradiotherapy 6 cycles TMZ
20	Glioblastoma	Not available	Not available	Male	55	Chemoradiotherapy 6 cycles TMZ

MGMT, methylguanine methyltransferase; IDH-1, isocitrate dehydrogenase-1; TMZ, temozolomide.

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