TOPIC REVIEW

Immune checkpoint inhibitor therapy for recurrent meningiomas: a retrospective chart review

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Abstract

Introduction Meningiomas that progress despite surgery and radiotherapy represent an unmet medical need. Expression of PD-1 and PDL-1 has been demonstrated in meningiomas and is proportional to tumor grade, suggesting a potential role for anti-PD-1/anti-PDL-1 inhibitor therapy. We explored the potential role of immunotherapy for recurrent meningiomas by describing progression-free survival (PFS) and overall survival (OS) in a single-center patient sample.

Methods This is a retrospective chart review of patients with meningioma who were treated with PD-1 inhibitors at UPMC Hillman Cancer Center. Any patient over age 18 who received immunotherapy was included in this study. Patients received treatment until development of disease progression, intolerable toxicities or adverse events, death, or oncologist decision. Serial radiographic assessments were made every 3–6 months.

Results Between January 2015 and November 2021, eight patients received anti-PD-1 therapy. All patients underwent tumor resection and radiosurgery, and four patients received prior systemic therapy. Six out of eight patients experienced symptomatic perilesional edema and three patients experienced exacerbation of seizures. Median PFS was 7 months (95% CI 1–24) and median OS was 1.75 years (95% CI 1.5–4.0). In patients with positive PD-1/PD-L1 expression, median PFS was 2 years and median OS was 3 years.

Conclusion Anti-PD-1 therapy was associated with a manageable safety profile in patients with recurrent meningiomas. Patients with WHO Grade III tumors and positive PD-1/PD-L1 expression were noted to have increased PFS and OS, suggesting a potential role for immunotherapy in these patients, but further studies are needed to investigate this in a larger patient population.

Keywords Nivolumab · Pembrolizumab · Immunotherapy · High grade meningioma · Recurrent meningioma

Introduction

Meningiomas represent one third of all central nervous system tumors and are the most frequently diagnosed primary intracranial tumors [1]. They originate from arachnoid cap cells within the arachnoid mater. Although the majority of these tumors are benign, their size and location intracranially can lead to significant morbidity and mortality [2]. The World Health Organization (WHO) classification of meningiomas includes three grades; I (benign), II (atypical), and III (malignant) [3]. The overall survival (OS) and progression-free survival (PFS) of each grade are 80–90% and 75–90%, 53–79% and 23–78%, and 14–34% with rapid progression, respectively [4]. Although surgical resection ± radiotherapy serve as the initial therapeutic approach and are typically able to control disease in patients with benign meningiomas, higher-grade tumors (WHO Grade II/III) are more likely to recur following this initial treatment. Many alternative agents, including chemotherapeutic agents, targeted drugs, angiogenesis inhibitors, and somatostatin analogues, have been studied but have not displayed clear evidence of lengthening PFS or OS in this subset of patients [5].
Checkpoint-inhibitors, along with other forms of immunotherapy, have been investigated as a potential treatment option in recent years [6]. Meningiomas are known to exhibit several immune checkpoint proteins, notably PD-1 and PD-L1 [4]. PD-L1-positive tumor cells bind onto PD-1 receptors on T cells and B cells to inhibit T-cell activation [6]. It has been discovered that the expression of these proteins, specifically PD-L1, is proportional to tumor grade, meaning that higher grade meningiomas express a greater amount of PD-L1 [7]. In addition, it has been shown that PD-L1 is predictive of poor overall survival and is associated with disease progression and recurrence [6, 8]. These findings suggest a potential role for anti-PD-1/anti-PD-L1 inhibitor therapy in the treatment of recurrent, high grade meningiomas. Most studies regarding this topic have demonstrated the presence of immune checkpoint proteins that may suggest the role of these therapies, but there are very few individual case reports of patients with observed regression of meningioma with immune checkpoint inhibitor therapy [9]. This retrospective chart review aims to explore the potential role of anti-PD-1 inhibitor therapy in the treatment of recurrent meningiomas by describing safety, PFS, and OS.

**Patient selection and methods**

The records of patients at University of Pittsburgh Medical Center Hillman Cancer Center between January 2015 and November 2021 were reviewed retrospectively between April 2021 and November 2021. The study was reviewed and approved by the University of Pittsburgh Institutional Review Board and designated as exempt under section 45 CFR 46.104(d)(4). Funding for use of anti-PD-1 therapy was provided by patients’ insurance or through the manufacturer’s patient assistance programs in patients whose insurance coverage was denied.

All patients above age 18 who were treated with anti-PD-1 therapy at any point in their disease course were included in this study. There was no limit on the number of prior or subsequent therapies. All patients had a tumor WHO grade of at least II or III at the time of immunotherapy initiation, received at least one dose of anti-PD-1 inhibitor therapy, and had at least one post-treatment radiographic follow-up. The immune checkpoint inhibitors used in this study were nivolumab and pembrolizumab, both of which are monoclonal IgG4 antibodies that target PD-1 [9]. Of the eight patients included in this study, seven patients received nivolumab 3 mg/kg intravenously every 2–4 weeks, and one patient received pembrolizumab 2 mg/kg every 3 weeks. Treatment was continued at these time intervals until development of PD, significant toxicity or adverse event, or physician decision. Toxicities were rated based on the Common Terminology Criteria for Adverse Events (CTCAE) [10]. Additionally, variables including tumor grade both at diagnosis and at immunotherapy initiation, comorbid conditions, tumor mutational burden and PD-1/PD-L1 status, and prior and subsequent therapies, performance statuses as defined by the Karnofsky Performance Status Scale (KPS) and the Eastern Cooperative Oncology Group (ECOG) were recorded.

The Response Assessment in Neuro-Oncology Working Group (RANO) criteria to assess for progression of disease was used in this chart review [11]. Progression of disease was defined as a radiographic increase in tumor size on MRI by greater than or equal to 25% or development of any new lesions, and stability of disease was defined as < 25% change in tumor size and no development of new lesions. Based on these definitions, PFS was defined as the time from the first day of immune therapy to the date of PD seen on MRI brain, and OS was defined as the time from the first day of immune therapy to the date of patient death. The primary aim of this study were to evaluate the PFS and OS of patients with recurrent meningioma who were treated with immunotherapy, and the secondary aims were to evaluate the toxicities and adverse outcomes associated with immunotherapy in these patients. Kaplan–Meier survival curves were created using MedCalc Statistical Software to illustrate PFS and OS and to calculate 95% confidence intervals.

**Results**

**Patient characteristics**

Between January 2015 and November 2021, eight patients with high-grade meningioma were treated with anti-PD-1 therapy. Seven patients were treated with Nivolumab, and one patient was treated with Pembrolizumab. Six of these patients were men (75%) and two were women (25%) with ages ranging from 38 to 79 (median 62.5). At the time of immunotherapy initiation, four patients had WHO Grade II tumors and four patients had WHO Grade III tumors. All target lesions at the start of immunotherapy initiation were > 10 mm in two dimensions. Three patients with WHO grade III tumors had positive PD-L1 expression, and one of these patients also had positive PD-1 expression. Two patients were PD-L1 negative, and the remainder were not tested. Median ECOG score was 2 and median KPS was 60. Patient characteristics are outlined in Table 1 and co-morbid conditions are outlined in Table 2.

**Prior therapies**

All eight patients underwent craniotomy for tumor resection along with radiotherapy as part of standard initial treatment. Four patients underwent involved field
Table 1  Patient characteristics

| Description                              | Value                                      |
|------------------------------------------|--------------------------------------------|
| Age                                      | Median 62.5 (38–79)                        |
| Male to Female                           | 6:2                                        |
| Grade III                                |                                            |
| Mutational burden (Ki-67):               |                                            |
| <5%                                      | 1                                          |
| 15–20%                                   | 1                                          |
| 30–40%                                   | 1                                          |
| 50–60%                                   | 1                                          |
| NF-2 mutation                            | 3                                          |
| PD-1/PD-L1 status                        | 2 PD-L1 strong positive, 1 PD-1 strong and PD-L1 focal weak, 1 negative |
| Grade II                                 |                                            |
| Mutational burden (Ki-67)                |                                            |
| 10–15%                                   | 2                                           |
| 15–20%                                   | 2                                           |
| NF-2 mutation                            | 1                                           |
| PD-1/PD-L1 status                        | 1 PD-1 and PD-L1 negative, 3 not tested    |
| Prior therapy:                           |                                            |
| Surgery                                  | 8                                           |
| Repeat surgery                           | 5                                           |
| Radiotherapy                             | 8                                           |
| Involved field radiation                 | 3                                           |
| Stereotactic radiosurgery                | 4                                           |
| Gamma knife/CyberKnife radiosurgery      | 4                                           |
| Intensity-modulated radiation therapy    | 1                                           |
| Systemic therapy                         |                                            |
| Bevacizumab                              | 1                                           |
| Everolimus                               | 1                                           |
| Bevacizumab + Everolimus                 | 1                                           |
| Ipilimumab + Interferon                  | 1                                           |
| Anti-PD-1 therapy                        |                                            |
| Nivolumab                                | 7                                           |
| Concurrent Bevacizumab                   | 3                                           |
| Concurrent Ipilimumab + radiosurgery     | 3                                           |
| Monotherapy                              | 1                                           |
| Pembrolizumab                            | 1                                           |
| Median time to start of immunotherapy from date of diagnosis | 6 years |
| Median duration of immunotherapy         | 1.75 years                                 |
| Survival analysis                        |                                            |
| Median PFS                               | 7 months (1–42 months)                     |
| Grade III PFS                            | 15 months (2–42 months)                    |
| Grade II PFS                             | 5 months (1–18 months)                     |
| PD-1/PD-L1 + PFS                         | 2 years (6–42 months)                      |
| Median OS                                | 1.75 years (1.5–4.5 years)                 |
| Grade III OS                             | 2.5 years (1.5–4.0 years)                  |
| Grade II OS                              | 1.5 years (1.5–4.5 years)                  |
| PD-1/PD-L1 + OS                          | 3 years (2–4 years)                        |

This table outlines data regarding patient characteristics including age, tumor grade and mutations, and prior therapies along with survival analysis of primary endpoints (PFS and OS).
radiation, four patients underwent stereotactic radiosurgery, four patients underwent gamma knife or CyberKnife radiosurgery. Five patients underwent multiple craniotomies throughout their disease course due to tumor recurrence. Prior systemic therapies included Bevacizumab (one patient), Everolimus (n = 1), Everolimus with Bevacizumab (n = 1) and Octreotide LAR (n = 1).

**Anti-PD-1 therapy**

One patient received Pembrolizumab and seven patients received nivolumab. Of the patients who received nivolumab, three were treated with concurrent Bevacizumab to minimize steroid requirements and control peritumoral edema, three were treated with concurrent ipilimumab and radiosurgery, and one received nivolumab monotherapy. The median time from date of diagnosis to date of immunotherapy initiation was 6 years, and the median duration of immunotherapy was 21 months. Three patients were noted to have radiographic progression within the first 2 months of immunotherapy initiation (37.5%); two of these patients received Nivolumab and were taken off treatment after development of radiographic and clinical progression, and one patient received Pembrolizumab and was continued on this despite development of interval radiographic progression because it was also being used for concurrent treatment of metastatic melanoma and lung adenocarcinoma in that patient. Seven out of eight patients were noted to have radiographic progression following immunotherapy initiation, and one patient continues to have stable disease.

**Survival analysis**

The aims of this study were to describe PFS and OS of patients with high-grade meningioma who were treated with immunotherapy. The median PFS was 7 months (95% CI 1–24) with a range of 1–42 months and the median OS was 1.75 years (95% CI 1.5–4.0) with a range of 1.5–4.5 years. Of the patients with WHO Grade III tumors at time of immunotherapy initiation, the median PFS was 15 months (range 2–42) and the median OS was 2.5 years (range 1.5–4.0). The remaining patients with WHO Grade II tumors had a median PFS of 5 months (range 1–18 months) and a median OS of 1.5 years (range 1.5–4.5 years). Three out of eight patients had tumors with positive PD-1 or PD-L1 expression; the median PFS for these patients was 2 years and the median OS was 3 years. Two patients died, and the other six patients remained alive by the time of data collection, with two patients continuing to receive active treatment with nivolumab. PFS and OS are displayed in Figs. 1 and 2, respectively.

**Toxicities and adverse events**

The most common treatment-related toxicities noted were symptomatic perilesional edema (n = 6) and exacerbation of seizure disorder (n = 3). Two patient experienced poor wound healing complicated by multiple infections at their craniotomy sites, and one of these patients suffered from right vertex and posterior left temporal lobe infarcts thought to be secondary to venous occlusion. Two patients experienced adverse effects of concurrent Bevacizumab treatment including lower extremity edema from proteinuria, cardiomyopathy, weight gain, and hypertension. Two patients died, one due to pneumonia and one due to multi-organ failure secondary to septic shock. Graded treatment-related toxicities and adverse outcomes are outlined in Table 3.

**Table 2 Co-morbid conditions**

| Co-morbid conditions                                      | Number of patients |
|----------------------------------------------------------|--------------------|
| Seizure disorder                                         | 7                  |
| Hypertension                                             | 5                  |
| Hyperlipidemia                                           | 2                  |
| GERD                                                     | 2                  |
| Diabetes Type II                                         | 2                  |
| Depression                                               | 2                  |
| Hypothyroidism                                           | 1                  |
| Coronary artery disease                                  | 1                  |
| Childhood ALL s/p prophylactic cranial radiation therapy  | 1                  |
| Prostate cancer s/p prostatectomy                        | 1                  |
| Metastatic melanoma                                      | 1                  |
| Stage I Lung adenocarcinoma                              | 1                  |

This table outlines the comorbid conditions of the patients included in this study.
Discussion

Meningiomas account for one third of all primary brain tumors and can be classified as WHO Grade I, II, or III [1, 3]. Typically, meningiomas are first treated with attempts at surgical resection and/or radiotherapy, though high-grade meningiomas are more likely to recur despite this initial treatment [5]. For meningiomas that recur after surgery and radiotherapy, there is no effective salvage therapy [12]. Because meningiomas have been shown to exhibit immune checkpoint proteins, including CTLA-4, PD-1, and PD-L1, immune checkpoint blockade has become a potentially promising treatment option for high-grade meningiomas, particularly given evidence that PD-L1 expression is proportional to tumor grade [4, 6, 7, 12]. The PD-1/PD-L1 pathway mediates immune system evasion in these tumors, and blockade of this pathway has been shown to improve overall survival for multiple solid tumors including urothelial cancer, squamous cell head and neck cancer, non-small-cell lung cancer, and melanoma [12–16]. A potential role for immune checkpoint blockade in the treatment of high grade, recurrent meningiomas has been suggested given the increased expression of immune checkpoint proteins (notably PD-L1) on higher-grade tumors and their association with decreased OS, though clinical evidence of efficacy of immune checkpoint inhibitor therapy for recurrent meningiomas is still scarce. One case report by Gelerstein et al. describes a patient whose meningioma decreased in size following treatment with nivolumab [9]. Our retrospective chart review, although a preliminary observation given the limited sample size, similarly suggests a potential role for immune checkpoint inhibitor therapy in recurrent, high grade, pre-treated meningiomas. Our findings suggest a potential correlation between tumor grade and PD-1/PD-L1 status, and by extension, the possibility that immunotherapy could benefit this specific subset of patients.

It is important to acknowledge several limitations of this study. Because it is a retrospective chart review of patients from a single institution, the study is subject to selection and sampling bias. In addition, the very small sample size makes it difficult to draw meaningful conclusions that are generalizable to a larger population, and the patient sample chosen for this study was heterogeneous with varying prior, concurrent, and subsequent therapies that may have affected the efficacy of the immunotherapy. Despite these limitations, this study demonstrates that immunotherapy is a potentially viable treatment option for patients with recurrent, pre-treated, high-grade meningiomas with a relatively manageable safety profile. However, because this study is limited by its sample size, further studies are necessary to investigate the use of immunotherapy agents in a larger sample of patients to determine which subset of patients would

| Toxicity                                | Grade 2 | Grade 3 | Grade 4 | Grade 5 | Total |
|-----------------------------------------|---------|---------|---------|---------|-------|
| Symptomatic perilesional edema          | 4       | 2       |         |         | 6     |
| Seizure                                 | 2       | 1       |         |         | 3     |
| Hypertension                            | 2       |         |         |         | 2     |
| Strokes                                 |         |         | 1       |         | 1     |
| Proteinuria                             | 1       |         |         |         | 1     |
| Cardiomyopathy                          | 1       |         |         |         | 1     |
| Craniotomy infection                    |         |         | 1       | 1       | 2     |
| Weight gain                             | 1       |         |         |         | 1     |
| Hypophysitis                            | 1       |         |         |         | 1     |
| Pneumonia                               |         |         |         | 1       | 1     |
| Sepsis                                  | 1       |         |         |         | 1     |

This table illustrates the various toxicities and adverse outcomes experienced by patients included in this study with ratings based on the Common Terminology Criteria for Adverse Events [10].
benefit most from immunotherapy and which specific anti-PD-1 inhibitors are most efficacious.

Author contributions Both Dr. PN and Dr. JD contributed to the study concept and design. Data acquisition was performed by Dr. PN, and data analysis was performed by both Dr. PN and Dr. JD. The first draft of the manuscript was written by Dr. PN, and both authors commented on and edited previous versions of the manuscript. Both authors read and approved the final manuscript.

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Data availability All data recorded and analyzed during this study are included in this manuscript and the associated Figures and Tables.

Declarations

Conflict of interest The authors of this retrospective chart review declare that no funds, grants, or other financial support was received during the composition of this manuscript. The authors report no conflict of interest.

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