Low-grade glioma (LGG) encompasses a heterogeneous group of tumors that is clinically, histologically and molecularly diverse. They are relatively uncommon, constituting 5 to 10% of all primary brain tumors. Despite this, they are significant in that they typically progress and lead to premature death. Over the last five years, our understanding of LGG has evolved significantly, with a shift from classification of these tumors based on histology towards stratification of risk based on molecular subtype (Figure 1). Not only does this reduce subjective error, but allows for more targeted therapy.

Treatment decisions are directed toward improving upon natural history while limiting treatment-associated toxic effects. Recent evidence has documented a utility for adjuvant chemotherapy with procarbazine/lomustine/vincristine (PCV) or temozolomide (TMZ) in the management of LGG. Treatment efficacy with PCV has been well documented in treating these gliomas, but comes at the cost of severe adverse effects. TMZ is a relatively newer treatment that allows for the combination of prolonged exposure and minor adverse effects, making it a promising alternative. However, with no prospective trials comparing the two, it is difficult to say if one is an adequate substitute for the other. In addition, tumor response to chemotherapy based on molecular profile is a primary focus going forward.

**METHODS**

A literature review was conducted to identify studies reporting patient response to PCV, TMZ, or a combination of chemotherapy and radiation therapy (RT). References for this review were identified by searches of PubMed between January 1, 2017 and May 1, 2017 (Figure 2).

Eligibility criteria included:
- Patients greater than 16 years of age
- Notation of LGG subtype
- Report of overall survival (OS)
- Report of progression-free survival (PFS)
- Treatment course

Class I, II, and III data were included. Figures including superimposed Kaplan-Meier curves were generated using DigitizeIt (Bormisof, Braunschweig, Germany).

**RESULTS**

19 papers, consisting of a cohort of 1,720 patients, were identified. Ten examined PCV or TMZ as a salvage agent at progression following RT, and were excluded from analysis. Median PFS and OS were primary outcomes (Figure 3).

Four studies evaluating PCV met criteria, comprising a cohort of 344 patients (median age 43.75 years, range 30.0-46.5). While patients with TMZ were 32.5 months (range 19.0-46.0) for PCV alone, 48.0 months for RT alone, and 124.8 months for combined PCV+RT. Reported OS was 120 and 94 for months for PCV alone and RT alone, respectively. Taal and colleagues reported PFS and OS of 35 months and 83 months, respectively, for patients with intact 1p/19q. They found a PFS of 67 months for patients with 1p/19q codelletion; median OS was not reached for patients in this cohort. Buckner and colleagues reported OS of 61.2 and 157.2 median months for patients with wild-type and IDH1, respectively. Toxicity was a significant issue in these patient populations. Buckner reported grade III and IV blood toxicity in 41.6% of 125 patients. In contrast, patients in the radiation-alone treatment group had 0.8% grade III and IV blood toxicity. Six studies evaluating TMZ met criteria, comprising a cohort of 933 patients with a median age of 41.5 years (range 30.0-49.0). While patients with TMZ were 46 months for RT alone and 31.0 months (PFS range: 21.8-45.6) for TMZ alone. Fisher and colleagues reported a PFS of 54 median months when administering TMZ in combination with RT. Wahl and colleagues reported PFS and OS of 58.8 and 116.4 months for 1p/19q codelleted patients, respectively. In terms of IDH1, median PFS and OS were 134.4 and 43.2 months for patients with mutant IDH1, respectively, and 21.6 and 7.2 months for wild-type IDH1, respectively.

TMZ chemotherapy was also accompanied by adverse effects in all six studies included for analysis. Toxicities encountered in all studies included myelosuppression and gastrointestinal complaints.

Our review is limited by constraints intrinsic to the literature reviewed, including different methods of reporting outcomes, treatment regimes, and patient populations. Data comparison is limited by confounding variables.

**CONCLUSIONS**

Based on our systematic review of the data, we suggest:
- In patients harboring a tumor with an unfavorable natural history, such as those with intact 1p/19q and wild-type IDH1, RT/TMZ plus adjuvant TMZ may be the best option.
- Conversely, patients with biologically favorable high-risk LGG are likely to derive the most benefit from RT and adjuvant PCV.

While there is a breadth of data available for both PCV and TMZ, the variable conditions of the studies limits the comparison of data. Prospectively head-to-head studies are needed to fully evaluate PCV versus TMZ in the treatment of patients with LGG. Additionally, as our understanding of these tumors based on molecular subtype grows, patient-specific targeted therapy is the objective.

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