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TOPIC REVIEW

The role of emerging therapy in the management of patients with diffuse low grade glioma

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Abstract

Question What is the role of immunotherapy/tumor vaccines in the treatment of low grade gliomas?

Target population Adult patients with newly diagnosed WHO grade 2 astrocytoma, oligo-astroctyoma, or oligodendroglioma.

Recommendations There is no evidence to support a recommendation in regards to the efficacy of immunotherapy or tumor vaccines for the treatment of low grade gliomas. It is recommended that patients be enrolled in properly designed clinical trials to assess immunotherapies and tumor vaccines for low grade gliomas.

Question What is the role of nutrition in the treatment of low grade gliomas?

Target population Adult patients with newly diagnosed WHO grade 2 astrocytoma, oligo-astroctyoma, or oligodendroglioma.

Recommendations There was no evidence to support a recommendation in regard to the efficacy of nutritional therapy for the treatment of low grade gliomas. It is recommended that patients be enrolled in properly designed clinical trials to assess the efficacy of nutrition for this target population.

Question Is there a role for alternative or targeted therapies in the treatment of low grade gliomas?

Target population Adult patients with newly diagnosed WHO grade 2 astrocytoma, oligo-astroctyoma, or oligodendroglioma.

Recommendation There was no evidence to support a recommendation in regard to the efficacy of targeted or alternative agents for the treatment of low grade gliomas. It is recommended that patients be enrolled in properly designed clinical trials to assess alternative and targeted therapies for this target population.

Keywords Low grade glioma · Immunotherapy · Nutrition · Alternative therapies · Anti-angiogenic therapy · Molecularly targeted therapy

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Emerging therapy rationale

The treatment of diffuse low grade gliomas (defined as WHO grade II astrocytoma, oligodendroglioma and mixed oligoastrocytoma for the purposes of this guideline) remains controversial. Since these tumors are typically slow growing, there has been interest in emerging or "alternative" therapies including immunotherapy and/or tumor vaccines, nutritional therapies and other alternative modalities to treat these neoplasms or at least attempt to prevent or slow their development into high grade neoplasms. The purpose of this paper is to systematically review the available evidence for the various emerging therapies in the treatment of low grade gliomas.

Emerging therapy methodology

Literature review

The following databases were searched from 1990 to 2012 using low-grade glioma and surgery relevant search MeSH and non-MeSH search terms: PubMed (National Library of Medicine, http://www.ncbi.nlm.nih.gov) was searched using Endnote® (Thomas Reuters, Inc. http://www.endnote.com) using the following key words: Low grade glioma, astrocytoma, oligoastrocytoma, oligodendroglioma, immunotherapy, tumor vaccine, nutrition, alternative therapies, antiangiogenic therapy, molecularly targeted therapy. Similar search strategies were used to search Cochrane Database of Systematic Reviews.

Article inclusion and exclusion criteria

For literature to be included for consideration, studies had to meet the following criterion:

- Be published in English
- Involve patients with newly diagnosed WHO grade 2 astrocytoma, oligo-astroctyoma, or oligodendroglioma
- Involve adult patients (age over 18) or provide isolated results for adult patients in a mixed cohort

Exclusion criterion:

- non-English publications,
- basic science papers,
- animal studies,
- manuscripts dedicated to pediatric gliomas
- manuscripts describing only malignant or high-grade glioma
- manuscript describing recurrent gliomas
- papers focusing exclusively on surgery, chemotherapy, radiation or anesthesia
- manuscripts focusing on Grade I tumors pylocytic astrocytoma (PCA), pleomorphic xantroastrocytoma (PXA), Primitive neuro-ectodermal tumor (PNET), ganglioglioma etc.

Study selection and quality assessment

Following broad screening for relevance, two independent reviewers evaluated citations and full text screening of potentially relevant papers using a priori criteria for data extraction on a standardized form. Disagreements were resolved with the involvement of a third reviewer, followed by primary re-review until agreement was achieved. Studies which met the eligibility criterion were extracted by one reviewer and this was then checked by a second reviewer. The quality of comparative studies using non-randomized designs was evaluated using eight items selected and modified from existing scales.

Evidence classification and recommendation levels

Both the quality of the evidence and the eventual strength of the recommendations generated by this evidence were graded according to a three-tiered system for assessing studies addressing diagnostic testing as approved by the American Association of Neurological Surgeons (AANS)/ Congress of Neurological Surgeons (CNS) Joint Guidelines Committee on criteria.

Conflict of interest

Low Grade Glioma Guidelines Task Force members were required to report all possible COIs prior to beginning work on the guideline, using the COI disclosure form of the AANS/CNS Joint Guidelines Committee, including potential COIs that are unrelated to the topic of the guideline. The CNS Guidelines Committee and Guideline Task Force Chair reviewed the disclosures and either approved or disapproved the nomination. The CNS Guidelines Committee and Guideline Task Force Chair may approve nominations of Task Force Members with possible conflicts and address this by restricting the writing and reviewing privileges of that person to topics unrelated to the possible COIs.

Emerging therapy scientific foundation

The authors reviewed 2500 publications including 2342 publications in PubMed and 158 in the Cochrane database. We identified only six papers which appeared to address the search criterion. After excluding three of these which did not meet search criterion after more detailed review, only three papers remained. The flow of the studies through the review process is illustrated in Fig. 1. A summary of studies reviewed and the class of evidence they represent is presented in Table 1.

No class I or class II evidence was identified which addressed the questions of interest. There was no objective evidence addressing the role of immunotherapy or tumor vaccines identified. However, we did find minimal Level III evidence which addressing the role of nutrition and alternative therapies for the care of low grade gliomas as noted below.

Nutrition

A single center retrospective study of 182 patients demonstrated that persistent hyperglycemia was independently associated with decreased survival, increased recurrence and increased malignant degeneration even after excluding

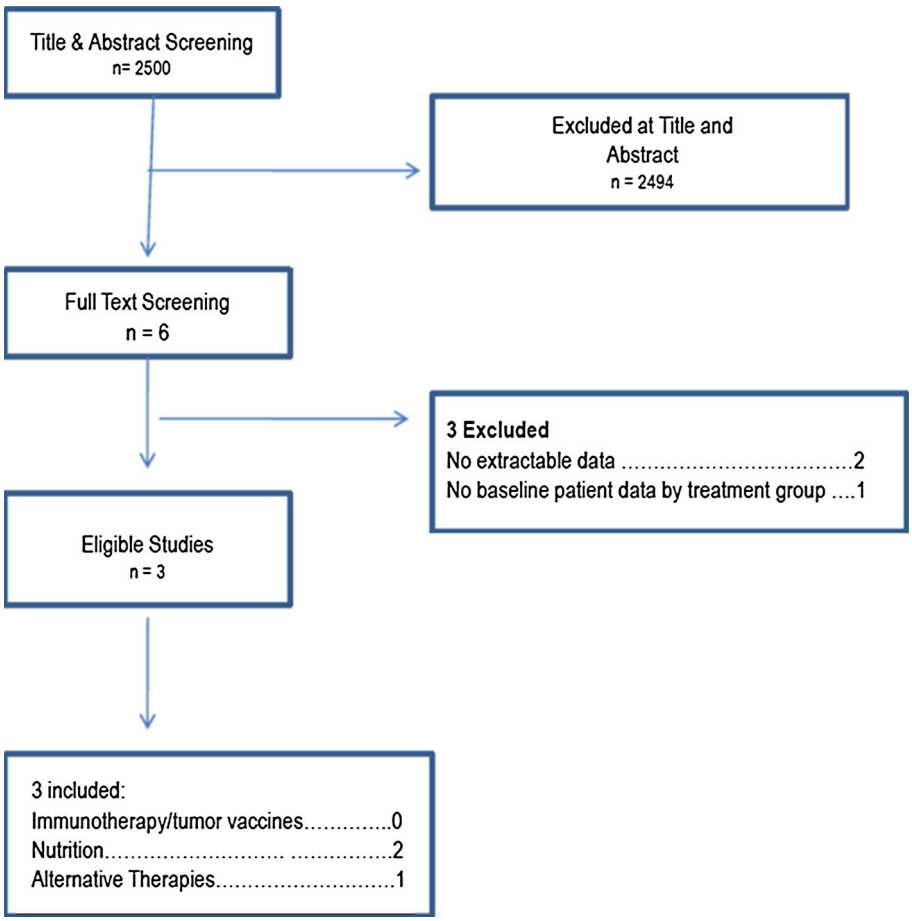

Fig. 1 The flow of studies through the review process

Table 1 Supporting Evidence

Author (year)	Description of study	Data class	Conclusions
Chaichana et al. (2010) [1]	Retrospective review of 182 patients with LGG at JHH 1996–2006	III	After correction for age, DM, and KPS, persistent hyperglycemia (defined as glucose > 180 ug/dl 3 or more times between 1 and 3 mo post-op) was associated with decreased survival ($p = 0.001$), increased recurrence ($p = 0.0001$) and increased malignant degeneration ($p < 0.001$)
DeLorenze et al. (2010) [2]	Retrospective review of self-reported nutrient questionnaire in Bay Area population based study of patients diagnosed with glioma 1991–1994 and 1997–2001	III	For patients with Gr II glioma, self-reported moderate (915.8–2118.3 mcg) intake of lycopene was associated with poorer survival than those with low intake (<915.8 mcg/d); while all patients with moderate (297.4–434.7 ug/d) folate intake had increased survival
Heese et al. (2010) [3]	Review of 621 patient questionnaires from 6 Neuro-Oncology centers in Germany	III	40 % of German patients with gliomas of all grades take complimentary therapies. This varied by age (young > old); Gender (F > M); and education (college > no college). Motivation was not dissatisfaction with conventional Tx, but a desire to do more

DM diabetes mellitus, *KPS* karnofsky performance score

all patients with diabetes and those on continued post-operative steroids [1]. Data obtained from a modified food-frequency questionnaire administered as part of a population based study suggested that the influence of anti-oxidants on survival was inconsistent [2]. Self-reported moderate intake of fat-soluble lycopene was associated with poorer survival

compared to low or high intake. Conversely, moderate intake of folate, was associated with greater survival. Assessment of actual plasma concentrations of the various nutrients assessed in the study was not performed. This adds to the complexity of understanding the role of various nutrients since differences in absorption may vary both among various nutrients as well as between individuals.

Alternative therapies

While no evidence for the efficacy of alternative or targeted therapies was identified, one group reported the results of questionnaires returned by 621 of 939 patients surveyed at 6 Neuro-Oncology centers in Germany [3]. This study revealed that more than 40 % of patients with low grade gliomas self- reported using complementary therapies. In general, there were significant differences in usage seen with respect to age (younger > older), gender (female > male), and education (higher educational level > lower educational level). However, analysis was aggregated among all gliomas and it was not possible to assess the differences in these practices between patients with different grades or histologies of glioma. Most patients appeared to use complementary therapies *in addition to* rather than *instead of* conventional treatment, and did so in the belief that they were doing something to complement the care of their physician, rather than because of distrust of their physician. However, data for all grades of gliomas were aggregated in this analysis and thus motivations and beliefs of patients with low grade gliomas could not be specifically assessed. Given the study methodology, it is likely that the 40 % figure represents an underestimate of actual practice.

Conclusions

There are no published objective data assessing the efficacy of immunotherapy or tumor vaccines on patients with low grade gliomas.

A single study provides Level III evidence demonstrating the adverse effect of early post-operative hyperglycemia on degeneration, recurrence and survival. However, there is little data on the effect of nutritional intervention or monitoring on patients with low grade glioma. Additional Level III evidence comes from a single questionnaire assessing the reported dietary intake of various antioxidants. The results suggested that moderate lycopene intake was detrimental, while moderate folate was beneficial. However there was no measurement of actual plasma concentrations of these antioxidants.

There is no published objective evidence assessing the efficacy of alternative therapies for patient with glioma. However, an observational study in Germany suggests that the use of such treatment is common in patients with low grade glioma and likely varies by age, gender, and educational achievement.

Key issues for future investigation

The treatment of low grade gliomas remains controversial. Since these tumors are typically slow growing, there has long been interest in emerging or "alternative" therapies including immunotherapy and/or tumor vaccines, nutritional therapies, and other alternative or targeted therapies to treat these neoplasms or at least attempt to prevent or slow their development into higher grade neoplasms. The lack of any Level I or Level II evidence addressing these issues and the dependence on questionnaires assessing recollections of past or current practices by patients and/or their caregivers rather than precisely measured and validated data reflects both the paucity of our current understanding of the role of these treatment modalities, as well as the complexity of research in these fields. It also suggests the need for future research.

In the last several years, immunotherapy appears to be making the transition from an "alternative therapy" primarily used in the treatment of melanoma and renal cell carcinoma to an accepted treatment. There is increasing recognition that many cancers actively suppress the immune system and a resurgence of interest in immunotherapy and tumor vaccines among both academic researchers and industry. This has taken various forms including but not limited to immunotoxins targeting tumor cells, humanized monoclonal antibodies targeting various immune cell subsets, peptide vaccines, as well as cellular therapies utilizing various autologous and allogeneic cells modified immunologically, genetically, or both. Although there have been no published studies of this patient population in the peer-reviewed literature, one co-author is currently completing a study addressing this patient population [4].

Similarly, increased recognition that tumors are metabolically different from normal cells has resurrected the field of cancer metabolism which had been languishing for several decades. Indeed, mutations of IDH 1 and IDH2, perhaps the most exciting findings in metabolomics, are more common in low grade gliomas than any other solid tumor. In addition to new interest in targeting tumor metabolism with pharmaceutical agents, which is covered elsewhere in this issue [5], there has been increasing interest in nutritional approaches to treating (and supporting) patients with glioma and other cancer. There are ongoing trials targeting glucose and ketone metabolism in higher grade gliomas. Given the longer survival (and thus increased time to treat), low grade gliomas might be considered a suitable subject for research on nutritional approaches and other non-cytotoxic approaches to cancer

treatment. However, in additional to logistical and financial challenges in treating this patient subpopulation (addressed below), the inconsistent findings regarding the role of anti-oxidant exposure of patients with low grade glioma [2] as well as the paradoxical findings implicating supplementary micronutrients in adverse outcomes in other cancers, demonstrate our current lack of understanding of this field. Indeed, ginko and other nutritional supplements have a known anti-coagulation effect that may exacerbate treatments to prevent DVTs and PEs, thus physicians must at the very least diligently inquire as to what nutritional supplements patients are taking. Hopefully, this will serve as the impetus to further study of the role of nutrition in patients with low grade glioma.

Immunotherapy, and nutrition are not the only emerging therapies worthy of study in low grade glioma. Studies in the use of electrical fields to impair cancer cell division and nanoparticles for diagnosis and treatment are ongoing in high grade glioma and may eventually be applied to low grade gliomas as well.

The field of alternative medicine has also gained importance as patients are living longer with disease, and the patients' views about medical treatment have become increasingly important both practically and politically. Given the limited efficacy of our current treatment armamentarium, increased survival (albeit limited) of patients with low grade glioma relative to those with high grade gliomas, and the prevalence of depression in patients with gliomas, it is not surprising that these patients are more likely to pursue alternative and/or complementary therapies than patients with higher grade gliomas. Given the 40 % usage reported in Germany, it is likely that the actual use is somewhat higher and may be higher in the US. Since patients are clearly utilizing these treatments (usually without their physicians' knowledge), it thus behooves neuro-oncology professionals to at least inquire from their patients what alternative treatments they partake in.

One significant challenge to research in this field in all the areas mentioned above is funding. In addition to the current challenges in obtaining research funding in this era of the sequestered NIH budget, the infrequency and rather long natural history of low grade gliomas compared to higher grade gliomas makes accrual to clinical trials much more difficult as well as expensive. The small numbers of patients at any single institution will likely necessitate multi-center collaboration for anything but small phase I studies. While the various mutli-center, multi-disciplinary consortiums have sponsored various therapeutic trials in the past in this patient population, the relative infrequency of low grade gliomas relative to other neoplasms of the brain and other organs lowers the perceived "impact" of such studies, making them less competitive for federal support. Likewise, the need to follow patients for longer than the 5 year duration of the standard federal grant cycle adds to the expense and complexity of these studies making them even less likely to get federal support. The role of private foundations such as the Susan B. Komen foundation in funding research in other fields (such as breast cancer) sets an example for the glioma field to strive for and some of these have already funded clinical studies of higher grade gliomas.

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