Taylor & Francis
Taylor & Francis Group

Expert Opinion on Pharmacotherapy

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ieop20

Choosing appropriate chemotherapy for diffusely infiltrating WHO grade II gliomas in adults

Alessia Pellerino, Luca Bertero, Roberta Rudà & Riccardo Soffietti

To cite this article: Alessia Pellerino, Luca Bertero, Roberta Rudà & Riccardo Soffietti (2020) Choosing appropriate chemotherapy for diffusely infiltrating WHO grade II gliomas in adults, Expert Opinion on Pharmacotherapy, 21:6, 613-615, DOI: 10.1080/14656566.2020.1714030

To link to this article: https://doi.org/10.1080/14656566.2020.1714030

Published online: 20 Jan 2020.

EXPERT OPINION ON PHARMACOTHERAPY
2020, VOL. 21, NO. 6, 613–615
https://doi.org/10.1080/14656566.2020.1714030

Taylor & Francis
Taylor & Francis Group

EDITORIAL

Choosing appropriate chemotherapy for diffusely infiltrating WHO grade II gliomas in adults

Alessia Pellerino[a], Luca Bertero [b], Roberta Rudà[a] and Riccardo Soffietti[a]

[a]Department of Neuro-Oncology, University and City of Health and Science Hospital, Turin, Italy; [b]Pathology Unit, Department of Medical Sciences, University of Turin, Turin, Italy

ARTICLE HISTORY Received 31 October 2019; Accepted 7 January 2020

KEYWORDS Chemotherapy; clinical trials; diffuse gliomas; IDH inhibitors; procarbazine/CCNU/vincristine; temozolomide

1. Introduction

New advances have been made in understanding the biology and treatment of diffuse gliomas, but a number of controversies regarding the management following surgery are still open. According to WHO 2016 the combination of two different molecular markers, such as IDH-1 and −2 mutation and 1p/19q codeletion, allows the stratification of lower grade gliomas into three different subtypes (oligodendroglioma IDH-1 and −2 mutated with 1p/19q codeletion, diffuse astrocytoma IDH-1 and-2 mutated lacking 1p/19 codeletion, and diffuse astrocytomas IDH wild-type) with different outcome in terms of overall survival (OS) [1]. Thus far, clinical trials on WHO grade II gliomas, including RTOG 9802 and EORTC 22033–26033, used clinical factors only to define the high-risk status (age ≥ 40, neurological symptoms, astrocytoma histology, tumor >4 cm of diameter, and incomplete resection), but did not include the assessment of the aforementioned molecular factors. With a modern approach, that includes these molecular markers, low-risk patients are considered those with IDH-1 and −2 mutations, with or without 1p/19 codeletion, who underwent a gross total or a supratotal resection: in these tumors, a watch-and-wait approach is still the standard of care. Conversely, IDH wild-type diffuse astrocytomas are often aggressive tumors and are now treated with adjuvant radiotherapy (RT) and chemotherapy regardless of the extent of resection: this applies in particular to the subgroup showing molecular alterations of glioblastoma, such as EGFR amplification and/or TERT promoter mutation an/or 7 +/10q- [2].

An adjuvant treatment in high-risk diffuse grade II gliomas is generally considered, but the impact differs within the molecular subtypes. The phase III RTOG 9802 [3] reported a significant advantage for the combination of RT and procarbazine, CCNU, and vincristine (PCV) chemotherapy: a subsequent secondary analysis has shown that oligodendrogliomas IDH mutated and 1p19q codeleted had the maximum benefit as compared to IDH mutated and 1p19q non codeleted diffuse astrocytomas, while no benefit for the addition of chemotherapy was observed in IDH wild-type diffuse astrocytomas [4]. An issue that will be investigated in EORTC 1635-IWOT trial (NCT03763422) is the role of watch-and-wait versus early radiation and chemotherapy in high-risk diffuse astrocytomas IDH mutated lacking 1p/19q codeletion.

Temozolomide (TMZ) is increasingly considered a replacement for PCV due to the lower myelotoxicity. A phase III CATNON trial in newly-diagnosed 1p/19 not-codeleted anaplastic (grade III) gliomas has demonstrated a benefit in OS when TMZ is administered in the adjuvant setting following RT as compared to radiation alone [5]. Thus far, it is still unclear whether TMZ is equal in terms of disease control as compared with PCV in lower grade gliomas [6]. This issue will be investigated in the phase III CODEL trial (NCT00887146), which is randomizing IDH mutated and 1p/19q codeleted oligodendrogliomas of both grade II and III to receive RT + PCV versus RT + TMZ.

The risk of neurocognitive impairment in long-term survivors after 8–12 years following RT has led a number of clinicians to postpone the use of RT in favor of an up-front chemotherapy. A retrospective study of the US National Cancer Database has reported that chemotherapy alone may confer a similar OS compared with chemoradiation [7], but the median follow-up is too short (4.6 years) to reveal a late effect of chemoradiation.

Two phase II single arm studies have investigated the role of up-front TMZ in high-risk grade II gliomas.

Wahl and colleagues reported a median PFS and OS of 4.2 and 9.7 years, respectively [8]. Similarly, the phase II AINO (Italian Association for Neuro-Oncology) study showed a PFS of 4.2 years and an OS of 9.8 years in oligodendrogliomas IDH-mutated and 1p/19q codeleted [9]. Interestingly, both studies demonstrated a median time of delay to RT of 5.8 and 8.2 years, respectively, suggesting that TMZ alone as initial treatment after incomplete surgery may represent an option in high-risk patients with oligodendroglioma. The majority of patients treated with up-front TMZ in the Italian study, who were MGMT methylated at first surgery, became unmethylated at reoperation, suggesting a chemotherapy-induced shift toward a more chemoresistant phenotype. Moreover, TMZ has been shown to increase the mutation rate of low grade gliomas [10], but thus far this does not seem to increase the risk of a malignant transformation.

CONTACT Riccardo Soffietti riccardo.soffietti@unito.it Department of Neuro-Oncology, University and City of Health and Science Hospital, Via Cherasco 15, Turin 10126, Italy

The recent phase III EORTC 26033 has shown that PFS of IDH mutated and 1p/19 codeleted oligodendrogliomas does not differ between either TMZ or RT as initial treatment, while in IDH mutated and 1p/19 not-codeleted diffuse astrocytomas PFS following initial TMZ is significantly lower than that after RT [11].

Although IDH-mutated diffuse gliomas have a better prognosis and a higher sensitivity to chemotherapy, the IDH protein may represent a druggable antigen. The IDH catalyzes the conversion of α-ketoglutarate in 2-hydroxyglutarate (2-HG) leading to an hypermethylation of chromatin with a proliferative effect on glioma cells [12]. New compounds have been investigated in preclinical models and are entering the clinical trial scenario, such as ivosidenib (AG-120) and enasidenib (AG-221), that are reversible selective inhibitors of IDH-1 and IDH-2 mutant enzymes, respectively. Vorasidenib (AG-881), a pan-IDH-1 and −2 inhibitor, with better blood-brain-barrier penetration, is a compound with documented activity in glioma patients. Mellinghoff et al have conducted a phase I trial (NCT02481154) with a dose-expansion arm (10 or 50 mg daily) in 52 patients with lower grade gliomas reporting 2% of minor response, 75% of stable disease, and 21% of progressive disease with an acceptable tolerability [13]. A recent phase 0/1 trial (NCT3343197) has confirmed the ability of this inhibitor to significantly reduce the level of 2-HG in human surgical samples of human gliomas [14]. Last, other ongoing phase I trials are evaluating safety and pharmacokinetics of different IDH inhibitors (including DS-1001b, IDH305, and BAY-1436032) (NCT03030066, NCT02381886, NCT02746081). Another ongoing anti-IDH strategy, that is under investigation, is the use of demethylating compounds, such as 5-azacytidine (NCT03666559).

An innovative approach is represented by the use of specific vaccines against IDH1 R132H mutated gliomas. The NOA-16 trial (NCT02454634) preliminarily reported the development of a mutation-specific T cellular (24/30 patients, 80%) or humoral (26/30 patients, 87%) immune responses that was not detectable before vaccination [15]. Similarly, the RESIST trial (NCT00054717) aims to evaluate the safety and the immune response following PEPIDH1M vaccine in recurrent grade II gliomas, as well as a Chinese trial on IDH1R132H-dendritic cell vaccine in Gliomas (NCT02771301): these trials are in active enrollment and preliminary results are not expected before the end of 2020.

2. Expert opinion

Traditional chemotherapy is an important treatment in diffuse gliomas. Most of the available drugs used in clinical practice are alkylating agents, whose efficacy is strongly correlated with the molecular profile of the tumor (i.e. IDH1/2 mutation, 1p/19q codeletion, and MGMT methylation). Up-to-date chemotherapy for patients with residual tumor after initial surgery is recommended either in association with radiotherapy in case of diffuse astrocytomas (IDH mutated or wild type) or alone in case of oligodendrogliomas as defined by WHO 2016 Classification. In the absence of clearcut data, the choice between PCV and TMZ still relies on physician's and/or patient's preference. Future trials should clarify the risk of minor cognitive deficit following conformal radiotherapy in patients surviving more than 10–15 years, and their impact on working capabilities and quality of life. With the improvement of neurosurgical tools, reoperation at recurrence is increasingly used, especially in patients who did not receive early radiotherapy, but the prognostic value is not clear thus far. Last, most diffuse gliomas tend to recur, and no effective chemotherapy is validated at recurrence.

The challenge in the coming years is the identification of molecular pathways that drive tumor progression and are druggable. Up-to-date inhibitors of IDH or BRAF mutations or TRK fusions appear the most promising; however, only well-designed clinical trials will be able to define the optimal sequence and combination of standard therapeutic options with new molecular agents.

Funding

This manuscript has not been funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

ORCID

Luca Bertero http://orcid.org/0000-0001-9887-7668

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Louis DN, Perry A, Reifenberger G, et al. The 2016 world health organization classification of tumors of the central nervous system: a summary. Acta Neuropathol. 2016;131(6):803–820.
•• **Recent WHO Classification of CNS tumors with the addition of a molecular level.**
2. Brat DJ, Aldape K, Colman H, et al. cIMPACT-NOW update 3: recommended diagnostic criteria for "Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV". Acta Neuropathol. 2018 Nov;136(5):805–810.
•• **Update ofWHO 2016 Classification on subdividing diffuse astrocytomas IDH wyld type into two prognostic subgroups.**
3. Buckner JC, Shaw EG, Pugh SL, et al. Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. N Engl J Med. 2016;374(14):1344–1355.
4. Bell EH, Won M, Fleming JL, et al. Updated predictive analysis of the WHO-defined molecular subgroups of low-grade gliomas within the high-risk treatment arms of NRG oncology/RTOG 9802. J Clin Oncol. 2019;37(15_suppl):2002–2002.
5. van den Bent MJ, Baumert B, Erridge SC, et al. Interim results from the CATNON trial (EORTC study 26053–22054) of treatment with concurrent and adjuvant temozolomide for 1p/19q non-co-deleted anaplastic glioma: a phase 3, randomised, open-label intergroup study. Lancet. 2017;390(10103):1645–1653.

6. Panageas KS, Iwamoto FM, Cloughesy TF, et al. Initial treatment patterns over time for anaplastic oligodendroglial tumors. Neuro Oncol. 2012 Jun;14(6):761–767.
7. Jhaveri J, Liu Y, Chowdhary M, et al. Is less more? Comparing chemotherapy alone with chemotherapy and radiation for high-risk grade 2 glioma: an analysis of the national cancer data base. Cancer. 2018;124(6):1169–1178.
8. Wahl M, Phillips JJ, Molinaro AM, et al. Chemotherapy for adult low-grade gliomas: clinical outcomes by molecular subtype in a phase II study of adjuvant temozolomide. Neuro Oncol. 2017;19 (2):242–251.
9. Rudà R, Pellerino A, Pace A, et al. Efficacy of initial temozolomide for high-risk low grade gliomas in a phase II AINO (Italian Association for Neuro-Oncology) study: a post-hoc analysis within molecular subgroups of WHO 2016. J Neurooncol. 2019;145 (1):115–123.
• **A post-hoc analysis of the efficacy of temozolomide alone with the molecular subtypes of WHO 2016.**
10. Johnson BE, Mazor T, Hong C, et al. Mutational analysis reveals the origin and therapy-driven evolution of recurrent glioma. Science. 2014;343(6167):189–193.
11. Baumert BG, Hegi M, van den Bent J, et al. Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma, A randomized phase III intergroup study by EORTC/NCIC-CTG/TROG/MRC-CTU (EORTC 22033–26033). Lancet Oncol. 2016;17(11):1521–1532.
12. Waitkus MS, Diplas BH, Yan H. Isocitrate dehydrogenase mutations in gliomas. Neuro Oncol. 2016;18(1):16–26.
13. Mellinghoff I, Penas-Prado M, Peters K, et al. ACTR-31. Phase 1 study of AG-881, an inhibitor of mutant IDH1 and IDH2: results from the recurrent/progressive glioma population. Neuro-Oncol. 2018;20(suppl_6):vi18.
• **A phase 0/1 study demonstrating that IDH inhibitors con impact the level of 2-HG.**
14. Mellinghoff I, Cloughesy TF, Wen PI, et al. A phase I, open label, perioperative study of AG-120 and AG-881 in recurrent IDH1 mutant, low-grade glioma: results from cohort 1. J Clin Oncol. 2019;37(15_suppl):2003–2003.
15. Platten M, Schilling D, Bunse T, et al. A first-in-man multicenter phase I clinical trial of the German Neurooncology Working Group evaluating a mutation-specific peptide vaccine targeting IDH1R132H in patients with newly diagnosed malignant astrocytomas. Neuro-Oncol. 2018;20(suppl_3):iii226–iii22.