Anaplastic gliomas: an emerging entity

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WHO grade III tumours or anaplastic gliomas comprise 6–10% of all newly diagnosed primary brain tumours in adults. They are differentiated into three major types: anaplastic astrocytoma (AA), anaplastic oligoastrocytoma (AOA) or anaplastic oligodendroglioma (AO). Although formally and clearly addressed, the diagnosis of both grade and type are areas of subjectivity in diagnostic neuropathology that are not clearly regulated in the current WHO classification. Problems occur in the differentiation between grade II and III astrocytoma, the classification of oligodendroglial tumours with necrosis, and the diagnosis of a mixed glioma, i.e., an oligoastrocytoma. Before the pathological entry criteria are unified tackling imaging questions may seem premature. However, closer correlations between histology and magnetic resonance imaging (MRI) parameters, such as perfusion-weighted imaging or MR spectroscopy or positron emission tomography (PET) may add to the decision on typing and grading in anaplastic tumours.

The current standard of care for first-line treatment in anaplastic gliomas is postoperative radio- or chemotherapy [1]. The prognostic impact of the surgical resection remains a field of controversy because of the scarcity of prospective clinical data. The best evidence available comes from the 5-aminolevulinic acid (ALA) trial in glioblastoma [2]. This, together with the most recent analysis of surgical data from the Neurooncology Working Group of the German Cancer Society (NOA)-04 trial, makes a strong case for the prognostic value of a gross total resection in anaplastic glioma as well [3]. The NOA trial did not uniformly use postoperative imaging only, but relied in part on the neurosurgical judgment.

The next steps have been regarded to define the role and optimal sequencing of combined-modality treatment focussing on radiotherapy and chemotherapy. Traditionally, the standard of care in oligodendroglial tumours has been biased by the conclusions drawn from the landmark work of Gregory Cairncross and David Louis. They introduced procarbazine, lomustine, and vincristine (PCV) chemotherapy and made the observation that patients with oligodendroglioma with 1p/19q co-deletions do better with PCV. Although this was the first prognostic molecular marker in neurooncology, it was discovered only later that improved sensitivity to therapy and not only to PCV is the reason for the relative success in treating these tumours [4]. Consequently, all large trials in the past few years have also focused on PCV. In contrast to glioblastoma [5] and a German trial for glioblastoma [6], it was felt that sequential radio- and chemotherapy, but not the immediate combination of both could improve outcome. After completion of three large randomised trials [3,7,8] the standard treatment in 2011 is regarded to be postoperative radio- or chemotherapy. The chemotherapy will most likely be temozolomide, as the NOA-04 trial documented a better tolerability compared with PCV [3]. However, conflicting data on the tolerability derive from a UK trial on the recurrent treatment of chemo-naive irradiated glioblastoma patients that showed a comparable or even better safety profile of PCV [9].

Similar to the glioblastoma treatment, the ongoing trial initiatives focus on the role of temozolomide in addition to radiotherapy in the newly diagnosed situation. One of the ongoing trials is even aimed at differentiating between the relevance of concomitant *versus* adjuvant temozolomide in non-co-deleted anaplastic glioma. The answer to this question would probably have an impact beyond the treatment of anaplastic glioma. At recurrence after a radiotherapy-containing primary treatment or radiotherapy alone, temozolomide is considered standard-of-care. The TAVAREC trial of the EORTC (26091) adds the vascular endothelial growth factor inhibitory antibody bevacizumab to temozolomide in the experimental arm of this trial in the first recurrence of low-grade and anaplastic glioma. Of note, the low-grade tumours must show a contrast-enhancing portion to be considered eligible. These tumours most likely share the same (non-favourable) prognosis with formal anaplastic glioma.

The other major development is in the field of molecular markers. Enriching patient populations with comparable prognosis via more objectively defined

molecular parameters, such as co-deletions of 1p/19q, hypermethylation of CpG residues in the promoter of the *O*^{6}*-methyl-guanyl-methyl-transferase (MGMT)* gene or mutations in codon 132 of the isocitrate dehydrogenase (*IDH*)1 gene, might help to differentiate between those who need maximal primary treatments and those who do better regardless of treatments with (late) side effects as one major concern. Therefore, the recent EORTC trial for newly diagnosed anaplastic glioma separates inclusion into the presence or absence of the 1p/19q co-deletion. This molecular parameter should be seen in its historical context. It was the first parameter to be found to be prognostic and at the time of the design of both the CATNON (EORTC 26054/22053) and the CODEL (EORTC 26081/22082) trials the only well-studied parameter in anaplastic glioma. Today, *MGMT* or even more so *IDH1* might be considered more relevant. IN a work from the German Glioma Network, the *IDH1* mutation separated two patient groups with even more pronounced differences in median overall survival than conventional histological features. Thus, *IDH1* analysis in high-grade astrocytomas is a more powerful prognostic marker than the current WHO classification describes. Importantly, patients with *IDH1* wild-type anaplastic astrocytoma survived for even less time than patients with *IDH1*-mutant glioblastoma [10]. As a consequence, one might consider combined radiochemotherapy with temozolomide [5] as therapy of choice, not only for patients with glioblastoma, but also anaplastic astrocytoma with wild-type *IDH1*.

In summary, anaplastic gliomas are an important group of brain tumours in the development of future molecularly targeted therapies and should therefore be in the main focus of academic and industrial drug development, which is aimed at efficacy and avoiding long-term side-effects.

Conflict of interest statement

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References

1 Wick W, Weller M. Classification and management of anaplastic gliomas. *Curr Opin Neurol* 2010;**18**:650–6.

2 Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen HJ; ALA-Glioma Study Group. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. *Lancet Oncol* 2006;**7**:392–401.

3 Wick W, Hartmann C, Engel C, et al.; for the Neurooncology Working Group (NOA) of the German Cancer Society. NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with PCV or temozolomide. *J Clin Oncol* 2009;**27**:5874–82.

4 Cairncross JG, Ueki K, Zlatescu MC, et al. Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. *J Natl Cancer Inst* 1998;**90**:1473–9.

5 Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005;**352**:987–96.

6 Neuro-Oncology Working Group (NOA) of the German Cancer Society. Neuro-Oncology Working Group (NOA)-01 trial of ACNU/VM26 *versus* ACNU/Ara-C chemotherapy in addition to involved-field radiotherapy in the first-line treatment of malignant glioma. *J Clin Oncol* 2003;**21**:3276–84.

7 Van den Bent MJ, Carpentier AF, Brandes AA, et al. Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomized European Organisation for Research and Treatment of Cancer phase III trial. *J Clin Oncol* 2006;**24**:2715–22.

8 Cairncross G, Berkey B, Shaw E, et al. Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: Intergroup Radiation Therapy Oncology Group Trial 9402. *J Clin Oncol* 2006;**24**:2707–14.

9 Brada M, Stenning S, Gabe R, et al. Temozolomide versus procarbazine, lomustine, and vincristine in recurrent high-grade glioma. *J Clin Oncol* 2010;**28**:4601–8.

10 Hartmann C, Hentschel B, Wick W, et al. Patients with IDH1 wild type anaplastic astrocytomas exhibit worse prognosis than IDH1-mutated glioblastomas, and IDH1 mutation status accounts for the unfavorable prognostic effect of higher age: implications for classification of gliomas. *Acta Neuropathol* 2010;**120**:707–18.