Management of diffuse glioma

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Summary

Diffuse gliomas constitute a diverse group of malignant brain tumors with varying aggressive course and heterogeneous survival. Although the mainstay of treatment of these distinct tumors is still based on the combination of surgery and classical therapeutic weapons such as radiotherapy and chemotherapy, important advances have been achieved over the past decades leading to meaningful improvements in survival times. In addition, recent progress in molecular profiling has allowed the identification of patients with better prognosis and more likely to respond to specific antitumor treatment. This is particularly true for grade II and III 1p/19q-codeleted gliomas, a subset of tumors in which data maturation after long-term follow-up have proved extremely important for accurate assessment of efficacy. This article aims at providing a review of the current specific antitumor treatment of diffuse glioma, particularly grade II and III glioma and glioblastoma, with special emphasis on the most relevant clinical trials conducted in these populations of patients.

Gliomas account for the vast majority, around 80%, of all malignant primary brain tumors [1]. These tumors arise from glial cells in the brain, particularly oligodendroglial and astrocytic lineage cells. Historically, and up to the previous 2007 World Health Organization (WHO) Classification, their classification and grading has been largely based on histopathologic features concerning similarities with putative cells of origin and presumed levels of differentiation [2]. In 2016, the WHO Classification has been updated incorporating well-established molecular features, notably 1p/19q-codeletion and mutations in isocitrate dehydrogenase (IDH) 1 or 2 genes [3]. The integration of both phenotypic and genotypic characteristics has prompted a better characterization of the spectrum of diffuse gliomas, allowing a better understanding of their distinct biological behaviours and consequent important implications in both prognosis and therapeutic approaches. Patients with diffuse glioma can present with symptoms and signs derived from either local parenchymal infiltration or compression of adjacent structures such as epileptic seizures, cognitive...
dysfunction and focal deficits, or from raised intracranial pressure. Guidelines on the symptomatic management of these patients have been recently published and this issue will not be further addressed in this article [4].

The aim of this article is to provide a comprehensive review of the current specific antitumor treatment of diffuse glioma, particularly grade II and III glioma and glioblastoma, with special emphasis on clinical trials that have led to improved of the pattern of care of these patients.

**Diffuse low-grade glioma**

The term diffuse low-grade glioma refers to WHO grade II diffuse infiltrating gliomas. They comprise different entities on the basis of specific histopathologic and molecular features (notably 1p/19q-codeletion and IDH mutations), and include oligodendroglioma, astrocytoma with mutations in IDH1 or IDH2 genes, and astrocytoma without IDH mutations [3]. Recognition of these diverse entities is important because their distinct behaviour and response to treatment has relevant implications for specific management.

Altogether, diffuse low-grade gliomas are rare brain tumors, accounting only for about 15% of all gliomas. Compared with high-grade gliomas, these tumors are generally diagnosed at younger ages, with epilepsy being the most frequent presenting symptom [5]. In addition, many cases are discovered incidentally during neuroimaging evaluations done for other reasons. Most patients with these slow but continuously growing tumors have longer survival than patients with grade III or IV gliomas. Thereby, treatment which is still not curative, is aimed not only at improving survival but also at minimizing treatment-related toxicity, particularly long-term effects on cognitive functions.

**Surgery**

Besides allowing definite histomolecular diagnosis, surgery constitutes by itself a critical therapeutic weapon in the management of patients with diffuse low-grade gliomas. The timing of surgery is still a subject of debate in some particular circumstances. In patients presenting with neurological symptoms or with large lesions and mass effect, the decision of undergoing surgery raises no doubt. However, the decision for surgery can be more questionable in asymptomatic patients with small incidentally discovered lesions [5,6]. In these latter cases, a conservative approach with close observation and delayed surgery until evidence of tumor growth can be advocated. To date, no prospective study has specifically addressed the impact on survival of early surgery as compared with initial observation and delayed surgical intervention. Available data are limited to retrospective observational studies, which suggest a trend toward improved survival with immediate surgery [7]. A population-based study recently compared these two approaches in patients with diffuse low-grade glioma. In this study, 153 patients from two Norwegian hospitals with different surgical treatment strategies were followed. Early surgical resection was favoured in one center (86% of patients) while watchful waiting after diagnostic biopsy was the preferred strategy in the other center (71% of patients). Interestingly, median survival times were significantly higher in the former center compared with the latter one (14.4 years vs. 5.8 years). This survival benefit observed with the early intervention strategy persisted after adjustment for molecular tumor characteristics [8,9].

Another important issue regarding surgery is the extent of resection. Apart from minimizing the risk of misdiagnosis linked to simple biopsy, a more extensive tumor resection also has a significant positive impact on survival outcomes. In the absence of randomized trials evaluating this issue, some observational prospective studies have demonstrated that more extensive surgeries are associated with improved survival rates. One of the largest studies included 216 patients with diffuse low-grade glioma, and found that those patients with an extent of resection exceeding 90% had a 5-year overall survival (OS) rate of 97% whereas those with lesser extent of resections had 5-year OS rates of 76% [10]. In addition to improvement in OS times, maximal safe resection has also been associated with a delay in both tumor progression and transformation to a higher grade [11,12]. On the basis of this evidence, authors recommend in general early maximal safe resection at the time of discovery of the suspected diffuse low-grade glioma.

**Radiotherapy**

Surgery alone is not curative, and further treatment with radiotherapy and/or chemotherapy is required at some point of the disease. However, the precise time and sequence of these therapies is still poorly defined and thereby the management of diffuse low-grade glioma patients after surgery remains somewhat challenging.

The EORTC 22845 phase III trial randomly assigned 314 patients with diffuse low-grade glioma to either early radiotherapy of 54 Gy in 1.8 Gy fractions or observation and deferred radiotherapy until the time of progression. After a median follow-up of about 8 years, early radiation therapy after surgery significantly lengthened the period without progression (5.3 years vs. 3.4 years), but did not improve OS times (7.4 years vs. 7.2 years) [13].

According to these results, and in an attempt to avoid potential long-term cognitive side effects, it is accepted to follow a policy of wait-and-see with close clinical monitoring and serial neuroimaging in diffuse low-grade glioma patients with more favourable prognosis, that is, young patients with complete tumor resection and favourable tumor molecular markers (mutated IDH, ideally 1p/19q-codeleted) [5,6]. However, it must be noted that in a large prospective series of 111 adult diffuse low-grade glioma patients younger than 40 years who had undergone neurosurgeon-determined gross-total resection,
52% of them suffered tumor progression 5 years after surgery. Factors associated with recurrence within the 5 years following surgery were tumor size larger than 4 cm, astrocytoma histology, and residual tumor larger than 1 cm on postoperative magnetic resonance imaging (MRI) [14]. These findings warrant convenient clinical and radiological follow-up even in those considered low-risk patients. On the other hand, adjuvant treatment with radiotherapy and chemotherapy should be advocated in patients who have a higher risk of tumor recurrence or progression, i.e., patients older than 40 years or with incomplete resection [5]. For many years, radiotherapy of 50 to 54 Gy in 1.8-2.0 Gy daily fractions has been the mainstay of treatment of diffuse low-grade glioma after surgery [15,16]. Two randomized studies evaluating radiation doses failed to demonstrate an increased survival with higher doses. In the EORTC 22844 trial, 379 adult patients with diffuse low-grade glioma were randomized to receive irradiation postoperatively or post-biopsy with either 45 Gy in 5 weeks or 59.4 Gy in 6.6 weeks. After a median follow-up of 6 years, no differences were found in OS rates (58% vs. 59%) and progression-free survival (PFS) rates (47% vs. 50%) between those two groups [15]. Importantly, in a sub-study specifically addressing quality of life, the patients who received high-dose radiotherapy tended to report lower levels of functioning and more symptom burden following completion of treatment, specially fatigue, insomnia and emotional functioning [17]. Similarly, a NCCC/G/RTG/ECOG randomized trial assigned 203 patients with diffuse low-grade glioma to receive low-dose (50.4 Gy in 28 fractions) vs. high-dose (64.8 Gy in 36 fractions) radiation therapy. At a median follow-up of 6.5 years, survival was non-significantly better with low-dose radiotherapy compared to high-dose treatment (94% vs. 85% at 2-years, and 72% vs. 64% at 5-years). Moreover, the incidence of grade 3 to 5 radionecrosis was slightly higher in the high-dose radiotherapy arm (5% vs. 2%) [16].

Chemotherapy
The role of adjunctive chemotherapy was assessed in the RTOG 9802 trial (NCT00003375), and it was not until recently, after long-term follow-up and data maturation, that adding chemotherapy to postoperative radiotherapy was shown to confer a clear survival benefit. In this study, 251 patients with high-risk diffuse low-grade glioma (patients younger than 40 years with subtotal resection, and patients aged 40 years or older with any extent of resection) were randomly treated with either postoperative radiotherapy alone or radiotherapy followed by six cycles of chemotherapy with procarbazine, lomustine and vincristine (PCV). Radiotherapy consisted of 54 Gy in 30 fractions in both groups. Results of this trial were first reported after a median follow-up time of 5 years. PFS but not OS was improved in patients receiving radiotherapy plus PCV chemotherapy compared to radiotherapy alone [18]. Interestingly, a subsequent analysis with a median follow-up of 12 years revealed significantly longer PFS and OS times among patients receiving both radiotherapy and combined chemotherapy than among those treated with radiation therapy alone. Median OS in the former group was 13.3 years vs. 7.8 years in the latter one, and PFS rates at 10 years were 51% vs. 21%, respectively. Importantly, the survival advantage of combining radiotherapy and chemotherapy was observed in all histologic subtypes, being the patients with oligodendroglioma histology the ones who benefited the most; in fact, the difference in OS times did not reach significance among patients with astrocytoma. Patients with tumoral IDH1R132H mutation determined by immunohistochemical testing had significantly longer PFS and OS than did those without the mutation, regardless of treatment. Moreover, among patients with the mutation, those who received radiotherapy plus chemotherapy and longer PFS and OS than did those who received radiation therapy alone [19]. Based on these findings, postoperative radiotherapy followed by chemotherapy with PCV has become the standard of care for these considered high-risk diffuse low-grade glioma patients. It must be noted that over the past decade, prior to the obtaining of the definitive results from the RTOG 9802 trial, PCV chemotherapy had been largely replaced by the alkylating agent temozolomide as the main cytosstatic agent in the treatment of diffuse low-grade glioma. A better safety profile and the conceived idea of a similar efficacy prompted this attitude [20]. The question whether temozolomide is as effective as PCV in this populations remains however unanswered. The non-randomized phase II trial RTOG 0424 evaluated radiotherapy with concomitant and adjuvant temozolomide in high-risk diffuse low-grade glioma patients, and preliminary results found improved OS rates compared with historical controls [21]. The currently ongoing phase III CODEL trial (NCT00887146), which aims to compare radiotherapy with concomitant and adjuvant temozolomide vs. radiotherapy with adjuvant PCV chemotherapy in patients with 1p/19q-codeleted anaplastic and diffuse low-grade gliomas, will resolve this interrogation. Another unsolved issue in the management of high-risk diffuse low-grade glioma is the role of upfront chemotherapy after surgery [6]. The goal of this particular approach, which might have special applicability in patients with 1p/19q-codeleted tumors due to their chemosensitivity [22], is to avoid radiation toxic effects. Some phase II studies have shown that temozolomide as single agent has notable antitumor activity [23]. The EORTC 22033-26033 phase III trial (NCT00182819) was recently conducted to investigate precisely whether initial temozolomide confers an advantage in outcome compared to standard radiotherapy with reduced long-term toxicity. For this purpose, 477 patients were randomized to receive radiotherapy of 50.4 Gy in 28 fractions or dose dense temozolomide (i.e. 75 mg/m2 once daily for 21 consecutive days every 28 days) for 12 months. Currently available data have shown, after a
median follow-up of 4 years, no significant difference in PFS between both groups. Median OS was not yet reached, thus further data maturation being needed [24]. Noteworthy, observed PFS seems to be inferior that obtained with the current standard of radiotherapy and chemotherapy. To summarize, the current standard of care for diffuse low-grade glioma consists of maximal safe resection followed by either close follow-up with serial neuroimaging in low-risk patients—younger than 40 years with complete resection—or radiotherapy and PCV chemotherapy for high-risk patients—older than 40 years or patients with subtotal resection. The management of patients with diffuse low-grade glioma lacking IDH mutations—that is, astrocytoma IDH wild-type—deserves to be mentioned apart. Patients with these tumors which are molecularly closer to grade IV astrocytoma or glioblastoma carry a more unfavourable prognosis. In these cases, it seems reasonable to treat patients with radiotherapy and concomitant and adjuvant temozolomide, similarly to glioblastoma [5].

Treatment options at recurrence, either still diffuse low-grade tumors or transformed to a higher grade, are limited to further surgery and/or radiotherapy if feasible, and rechallenge with the initial chemotherapy or administration of alternative cytostatic agents not previously used. In this context, the EORTC TAVAREC trial (NCT01164189) needs to be mentioned. This phase II study was conducted on patients with recurrent grade II and III non 1p/19q-codeleted gliomas, who were randomly assigned to receive salvage chemotherapy with temozolomide alone or combined treatment with temozolomide and the antiangiogenic agent bevacizumab. Preliminary results have shown that the addition of bevacizumab to temozolomide does not improve survival (12-month OS rates of 61% in the temozolomide group vs. 55% in the combined temozolomide plus bevacizumab group), regardless of IDH mutational status [25].

**Anaplastic glioma**

Similarly to what has been previously described for diffuse low-grade glioma, anaplastic or WHO grade III diffuse gliomas can be divided into three main entities according to their morphologic and molecular features: anaplastic oligodendrogliomas or 1p/19q-codeleted tumors, and astrocytomas with or without IDH mutations [3]. This analogy, in addition to similarities in outcome and treatment sensitivity among grade II and III tumors of the same lineage, illustrates the fine line that gradually separates diffuse low-grade from anaplastic gliomas, as well as the marked differences in the natural history of tumors according to IDH mutation.

Anaplastic glioma account for about 10% of all glioma, and usually occur at more advanced ages than diffuse low-grade glioma [1]. Their specific management consists also in a combination of surgery, radiotherapy and chemotherapy, with specific variations depending on particular molecular characteristics.

**Surgery**

Despite the lack of randomized trials investigating the impact of resection on outcome, there is a general agreement that surgery should consist, when feasible, on maximal resection [26]. In addition to lessons derived from glioblastoma and diffuse low-grade glioma, data from large clinical trials conducted in this population support this approach [27-29].

**Radiotherapy and chemotherapy**

Following surgery, the main adjuvant therapy has historically consisted on radiotherapy. Again, the exact dosage has not been questioned in a randomized study, and the total dose of 60 Gy delivered in 1.8 Gy fractions has been traditionally considered the standard practice.

The initial results of two large phase III trials conducted on formerly known anaplastic oligodendroglioma or oligoastrocytoma established radiotherapy as the standard therapy for such patients [27,28]. The RTOG 9402 study (NCT0002569) randomly assigned 291 patients to receive either up to 4 cycles of intensified PCV chemotherapy followed by radiotherapy (59.4 Gy in 33 fractions of 1.8 Gy) or immediate radiotherapy alone after surgery [28]. Simultaneously, the EORTC 26951 trial (NCT00002840) randomized 368 patients to either 59.4 Gy or radiotherapy in 33 fractions alone or to the same radiation therapy schema followed by 6 cycles of standard PCV chemotherapy [27]. The initial results obtained after a median follow-up of 5 years showed, in both studies, an increase in PFS in the group of patients additionally receiving PCV chemotherapy (RTOG 9402: 2.6 years vs. 1.7 years; EORTC 26951: 23 months vs. 13 months), but failed to demonstrate an improvement in OS (RTOG 9402: 4.9 years vs. 4.7 years; EORTC 26951: 40.3 months vs. 30.6 months) [27,28]. Some time later, after a 12-year follow-up period, results were updated and revealed improved survival outcomes with the addition of PCV to radiotherapy in patients with 1p/19q-codeleted tumors [30,31]. In the RTOG 9202 trial, observed median OS was 14.7 vs. 7.3 years in patients treated with the combination of PCV and radiotherapy vs. radiotherapy alone, respectively [30]. Similarly, median OS was not reached in the PCV plus radiation therapy group vs. 112 months in the radiotherapy alone group in the EORTC 26951 study [31].

Subsequent analysis have suggested the role of IDH mutation, CpG island methylated phenotype and 0-6-methyl-guanine DNA methyltransferase (MGMT) promoter methylation as predictive markers for benefit for adjuvant PCV chemotherapy [32,33]. Importantly, in both studies, patients with non 1p/19q-codeleted tumors exhibited worse prognosis, and impact of adding chemotherapy to radiotherapy was null (RTOG 9402: 2.6 years vs. 2.7 years; EORTC 26951: 25 months vs. 21 months) [30,31]. Based on these results, postoperative radiotherapy and chemotherapy with PCV constitutes the current standard of care for patients with 1p/19q-codeleted anaplastic glioma, that is,
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anaplastic oligodendrogliaoma. Whether PCV chemotherapy should be administered before or after radiotherapy is uncertain. However, because standard PCV after radiotherapy was much better tolerated than intensified PCV before radiotherapy, the former order is preferred.

The question that arises at this point, in the era of temozolomide, is which is the optimal chemotherapeutic regimen: PCV or temozolomide. This controversy remains unsolved; some studies suggest that outcomes might be similar with both cytostatic regimens [34,35]. The previously mentioned CODEL trial should ideally help clarifying this issue.

Moreover, patients with 1p/19q-codeleted anaplastic gliomas treated with radiotherapy and PCV are at risk of neurocognitive deterioration because of their prolonged overall survival. Thus, another yet unanswered question is whether treating these patients with PCV alone and deferring radiation until tumor progression could reduce the risk of cognitive deterioration without impairing overall survival. An ongoing ANOCEF randomized phase III trial (POLCA trial; NCT02444000) is precisely addressing this issue.

The abovementioned RT0G 9402 and EORTC 26951 trials failed to show a benefit of additional PCV chemotherapy in non 1p/19q-codeleted anaplastic glioma, that is, in anaplastic astrocytoma. Recently, the interim analysis of the CATNON trial (EORTC 26053-22054; NCT00626990) has found that adjuvant temozolomide chemotherapy is associated with a significant survival benefit in patients with newly diagnosed non 1p/19q-codeleted anaplastic glioma. This is a phase III trial in which 745 patients were assigned to receive radiotherapy (59.4 Gy in 33 fractions of 1.8 Gy) alone or with adjuvant temozolomide (150-200 mg/m²/day for 5 consecutive days every 28 days for up to 12 cycles), or to receive radiotherapy with concurrent temozolomide (75 mg/m²/day) with or without adjuvant temozolomide. The interim analysis of the study has revealed a 5-year OS rate of 55.9% with adjuvant temozolomide vs. 44.1% in patients who did not receive adjuvant chemotherapy. Median OS was not reached in the first group and was 41.1 months in the second one [36].

Mature results, which will clarify the role of concurrent temozolomide as well as the predictive value of IDH1/2 mutations, will be of practical importance since they may be practice changing. The doubt whether administering 6 cycles of adjuvant temozolomide instead of 12 is equally effective will remain an open question.

Finally, anaplastic astrocytoma without IDH mutations are known to be biologically distinct from IDH mutated tumors. From a prognostic point of view they are more similar to glioblastoma. On the basis of this reality, it is commonly recommended to treat these patients similarly to those with glioblastoma, that is, radiotherapy with concurrent and adjuvant temozolomide.

Glioblastoma

Glioblastoma or WHO grade IV astrocytoma is the most frequent malignant primary brain tumor in adults. It accounts for about 50% of gliomas, with an estimated annual incidence of 3–5 new cases per 100,000 people [1]. These figures, along with the dismal prognosis of this rapidly evolving disease, explain why a major part of research in neuro-oncology is focused on this type of diffuse glioma.

Newly diagnosed glioblastoma

In the absence of a contemporary curative treatment, the current standard of care for patients with newly diagnosed glioblastoma consists on the combination of maximal surgical resection, radiotherapy and concomitant and adjuvant chemotherapy [37].

Surgery

Surgical resection, when feasible, remains the initial treatment of choice for glioblastoma. Apart from providing tumor tissue for definite histomolecular diagnosis and leading to rapid relief of symptoms, tumor debulking constitutes by itself the first therapeutic step. Maximal safe resection with preservation of neurologic functions is the main goal. If tumor is located in eloquent areas and thus resection is not feasible, biopsy remains the alternative for diagnostic purposes. While a small prospective trial showed that extensive surgery was associated with increased survival as compared with needle biopsy [38], no other randomized trials have specifically addressed whether complete resection confers improved outcomes compared with lesser amounts of resection. However, extent of resection has consistently emerged as a strong independent prognostic factor in both large observational studies and clinical trials [37,39]. A recent survival prediction model for patients with newly diagnosed glioblastoma suggests that there is a survival advantage with any degree of resection, based on the finding of a continuous relationship between extent of resection and survival [40]. This argues against the practice of withholding surgery based on the belief that failure to achieve some predefined extent of resection threshold will negate potential survival benefits of surgery, and supports the widespread recommendation of performing, if feasible, maximum surgical resection in preparation for adjuvant therapy.

Radiotherapy and chemotherapy

Because glioblastoma are highly infiltrating tumors with unclear margins they are not amenable to complete resection, and persistence of residual tumor cells warrants further complementary treatment [3]. Again, radiation therapy has been for long time the backbone of postsurgical treatment [41]. Considering the predominant local recurrence patterns and the lack of a survival benefit, initial whole-brain radiation protocols have evolved to focal fractionated radiotherapy schemas, with standard doses of 60 Gy administered in 2 Gy fractions [42].
Hyperfractionated schedules or higher total doses (i.e. 70 Gy) have not demonstrated survival advantages, and are more likely to cause central nervous system toxicity [43]. Chemotherapy with temozolomide, an alkylating pro-drug that delivers a methyl group to purine bases of DNA resulting in transcription disruption and cell death, constitutes since 2005 the third mainstay of current standard treatment for newly diagnosed glioblastoma patients [37]. In the EORTC 26981-22981/NCIC CTG CE.3 phase III clinical trial 573 patients with newly diagnosed glioblastoma were randomly assigned to receive radiotherapy alone (60 Gy of fractionated focal irradiation in daily fractions of 2 Gy given 5 days per week) or radiotherapy plus continuous daily temozolomide (75 mg/m² per day, daily from the first to the last day of radiotherapy) followed by 6 cycles of adjuvant temozolomide (150–200 mg/m² for 5 days during each 28-day cycle). The median survival was 14.6 months with radiotherapy plus temozolomide and 12.1 months with radiotherapy alone. Although modest, this 2-month increase in survival was clinically meaningful and retained statistical significance [37]. At longer follow-up, the survival benefit of adding temozolomide to radiotherapy became more evident, with OS rates at 2 and 5 years rising from 10.9% to 27.2% and 1.9% to 9.8%, respectively [44]. Importantly, combined treatment with radio-chemotherapy had an acceptable tolerance and did not carry a negative impact on health-related quality of life. This study confirmed the role of MGMT promoter methylation as a major favourable prognostic factor as well as a predictor of response to treatment with temozolomide. MGMT is a DNA repair enzyme that counteracts chemotherapeutic cytotoxicity of alkylating agents. The silencing of the MGMT gene by promoter methylation results in reduced DNA repair activity and renders tumor cells more sensitive to this alkylating cytostatic agent [45].

This current multimodal standard of care for patients with newly diagnosed glioblastoma consisting on maximal safe resection followed by radiotherapy with concomitant and adjuvant temozolomide, irrespective of IDH genetic status, has remained unchanged over the last 13 years. Interestingly, large series and results from recent clinical trials suggest a mild increase in survival up to 16–17 months [46,47]. This hypothetical improvement in survival needs to be confirmed, and some key factors could contribute to this issue.

Technical advances in neuroimaging and neurosurgical proceedings may have a role, as fluorescence-guided surgery with 5-aminolevulinic acid and intraoperative MRI have been shown to improve the extent of surgical resection [48-50]. In addition, the learning curve for the combined radio-chemotherapy treatment might constitute a solid argument for the hypothetical better outcomes despite unchanged therapeutic approach. Particularly, the recognition of the phenomenon of pseudoprogession precludes avoiding premature and inappropriate discontinuation of an effective treatment with adjuvant temozolomide [51]. This concept of pseudoprogession refers to a subacute treatment-related inflammatory effect that mimics tumor progression on MRI. It typically appears within 3 months after completing radiotherapy, and spontaneously improves or stabilizes thereafter while continuing with the same chemotherapy with temozolomide [52] (figure 1). The real frequency of this treatment-related change is unknown, but could arrive at

**Figure 1**
Pseudoprogession phenomenon in a 35 year-old woman with newly diagnosed glioblastoma without mutation in IDH1/2 and with methylated MGMT promoter. A. Pre-surgery MRI. B. Early postoperative MRI. C. MRI obtained 1 month after RT-TMZ. D. MRI obtained 3 months after RT-TMZ. E. MRI obtained 6 months after RT-TMZ. F. MRI obtained 12 months after RT-TMZ. MRI: magnetic resonance imaging; RT-TMZ: radiotherapy and concomitant Temozolomide
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up to 30% according to some retrospective series [53,54]. Moreover, the likelihood of pseudoprogression is higher among patients with methylated MGMT promoter than in those with non-methylated tumors [55]. No clinical nor imaging feature can firmly distinguish between pseudoprogression and true progression. Hence, to avoid misinterpretation of neuroimaging changes within the first 12 weeks after radiotherapy completion, the Response Assessment in Neuro-Oncology Working Group proposed that in that period progression can only be determined if the majority of the new enhancement is outside the radiation field or if there is pathologic confirmation of progressive disease. On the contrary, if pseudoprogression is suspected, patients should be continued on their planned adjuvant chemotherapy with temozolomide [56].

Despite lack of evidence, continuing adjuvant treatment with temozolomide beyond 6 cycles is a common practice based on the belief that sustained treatment might help maintaining control of the disease. Analyses from retrospective small series have yielded disparate results, with some of them suggesting a benefit on survival without increased toxicity and others reporting no differences in outcome [57-60]. A recent meta-analysis of four randomized trials for newly diagnosed glioblastoma has addressed specifically this issue. Six hundred and twenty-eight patients who were progression free 28 days after the cycle 6 were included in the pooled analysis and stratified into two groups: those treated with 6 cycles and those who continued beyond that threshold. Prolonged treatment was associated with mild improvement in PFS, especially in patients with methylated MGMT promoter, but it was not shown to increase OS [61]. These results do not support the practice of prolonged adjuvant temozolomide, although further prospective studies might be needed to rigorously assess this issue.

Other alternative dosing schedules of temozolomide have not been demonstrated more effective in comparison with the standard one. Concretely, the RTOG 0525 phase III trial (NCT00304031) compared the standard adjuvant schedule of 150-200 mg/m² days 1 through 5 of a 28-day cycle against a dose dense protocol consisting on 75-100 mg/m² for 21 consecutive days of a 28-day cycle, and no therapeutic benefits were detected for the dose dense regimen [62].

Other therapies

Bevacizumab is a humanized monoclonal antibody that inhibits tumor angiogenesis by targeting vascular endothelial growth factor A. The usefulness of this agent was initially investigated in patients with recurrent disease, with some positive results that led to approval by US regulatory authorities in this setting. Despite promising results in a previous phase II trial [63], its beneficial use as upfront therapy in combination with standard radio-chemotherapy was not further confirmed in two large randomized phase III trials [46,47]. The AVAglio (NCT00943826) and RTOG 0825 (NCT00884741) studies evaluated the addition of bevacizumab to standard radiotherapy with concomitant and adjuvant temozolomide in 921 and 637 patients with newly diagnosed glioblastoma, respectively. Both studies showed similar outcome results. Treatment with bevacizumab was significantly associated with increased PFS (10.6 vs. 6.2 months in the AVAglio trial; and 10.7 vs. 7.3 months in the RTOG 0825 trial). However, OS times did not differ between patients treated with bevacizumab compared with those receiving placebo (16.8 vs. 16.7 months in the AVAglio trial; and 15.7 vs. 16.1 months in the RTOG 0825 trial) [46,47].

In a retrospective analysis of the AVAglio trial, the tumor samples from 349 patients were analysed for gene expression patterns and correlated with outcome. Findings from this study suggest that patients with IDH1 wild-type proneural glioblastoma may derive a survival benefit from first-line bevacizumab [64]. Based on this evidence, authors do not recommend the use of bevacizumab in addition to standard radio-chemotherapy with temozolomide in patients with newly diagnosed glioblastoma. Other antiangiogenic therapies have also failed to demonstrate a survival benefit in this population.

Tumor treating fields (TTFields) have emerged as a novel available treatment for patients with newly diagnosed glioblastoma in the post-radiotherapy setting [65]. This therapeutic approach consists on the continuous delivery of low-intensity, intermediate-frequency (200 kHz) alternating electric fields via transducer arrays applied to the shaved scalp. The antitumor effect is achieved by disrupting the mitotic spindle formation ring metaphase and causing dielectrophoretic movement of polar molecules during cytokinesis, thus resulting in mitotic arrest and cell apoptosis [65,66]. Results from an unblinded randomized phase III trial (EF-14; NCT00916409) comparing TTFields plus temozolomide vs. temozolomide alone after radiotherapy and concomitant temozolomide in newly diagnosed glioblastoma patients with stable or responding disease demonstrated a significant improvement in survival with the experimental therapy. The EF-14 trial was stopped early because of results favouring the intervention at the time of planned interim analysis, and the final analysis of this study has recently confirmed a gain in survival with the TTFields therapy: median OS of 20.9 vs. 16.0 months, and median PFS of 6.7 vs. 4.0 months. Electric fields therapy was found to be safe, with the most common adverse events consisting on mild to moderate skin reactions that were typically responsive to local steroids and rarely required treatment discontinuation [67]. With the caveat that the unblinded design could have led to biased health-promoting behaviours and other practical inconveniences or controversies such as cost-effectiveness [68], this novel therapeutic approach could represent a paradigm shift in cancer treatment in general and a new standard of care for selected patients with newly diagnosed glioblastoma in particular [66].
Recurrence glioblastoma

Treatement of patients with recurrent or progressive glioblastoma is challenging because of the lack of a standard of care and the limited therapeutic alternatives. These include reoperation, reirradiation and systemic antitumoral therapies, all of which can benefit selected patients. Given the lack of data from prospective randomized trials supporting a particular approach, treatment decisions at this stage of the disease should be individualized taking into account several key factors such as neurological and performance status, quality of life, prior therapies and time interval before recurrence, pattern of recurrence, extent of the tumor and peritumoral edema, and steroid toxicity.

In patients with localized recurrent tumors not involving eloquent areas surgery might be considered, especially when complete or near-complete resection can be achieved. Such aggressive resections have been suggested to maximize survival and even overcome the negative effect on outcome of an incomplete initial resection [69,70]. However, following surgery patients should receive further systemic therapy. The role of reirradiation in recurrent glioblastoma is also uncertain. Patients with small-volume tumors, recurrences located outside the initial radiation field, and otherwise good prognosis factors, might be candidates for this therapeutic alternative, especially if there are any contraindications for further systemic therapy [71,72].

Different cytostatic and antiangiogenic agents have been investigated in the setting of recurrent disease. However, no significant clinical benefit has been observed with any particular therapy. Nitrosourea such as lomustine, carmustine or fotemustine, were commonly used in the pre-temozolomide era, and today still constitute a reasonable option after failure to first-line chemoradiotherapy. They have shown some degree of activity, with survival times around 8 months [73].

Rechallenge with temozolomide has been studied in retrospective series and single-arm prospective studies. Different dosing regimens have been evaluated, with no real differences among them. Patients who have relapsed some time after completion of adjuvant temozolomide and especially those with methylated MGMT promoter appear the ones to benefit the most from this retreatment option [74] (figure 2).

According to antiangiogenic therapy, the original non-comparative phase II trials that first evaluated treatment with bevacizumab (10 mg/kg every 2 weeks) in patients with recurrent glioblastoma demonstrated remarkable radiographic responses in up to 30–60% of patients, and 6-month PFS rates ranging from 30 to 50% [75-78]. Although no direct impact on OS was observed, these results led to the rapid approval of bevacizumab by the US Food & Drug Administration. The European Medicines Agency rejected its approval due to the lack of controlled data. However, and despite the lack of a demonstrated survival benefit, this antiangiogenic agent is widely employed in the setting of glioblastoma recurrence (figure 3). Apart from its assumed antitumor action, its corticoid-like effect has a rapid and positive impact.
impact on neurologic symptoms and quality of life that supports its use in selected patients. When possible, delaying the use of bevacizumab and seeking alternative agents is an accepted strategy that relies on the observations that there is no effective treatment after bevacizumab failure and that deferring its use is not associated with diminished efficacy [79,80].

The first randomised controlled phase II trial of bevacizumab in recurrent glioblastoma (BELOB trial; NTR1929) was conducted in the Netherlands. One hundred and fifty-three patients were randomized to receive oral lomustine alone (110 mg/m² every 6 weeks), intravenous bevacizumab alone (10 mg/kg every 2 weeks), or combination treatment with lomustine (90–110 mg/m² every 6 weeks) and bevacizumab (10 mg/kg every 2 weeks). The median OS was 8 months for both single-agent groups and 12 months for the combination treatment group [81]. However, these encouraging results of the combination of lomustine and bevacizumab could not be later confirmed in an adequately powered randomised phase III trial [82]. This EORTC 26101 trial (NCT01290939) explored the combination of bevacizumab and lomustine vs. lomustine alone in 437 patients with first progression of a glioblastoma. Results of this study showed an increase in PFS times (4.2 vs. 1.5 months, respectively) without significant impact on OS (9.1 vs. 8.6 months, respectively) [82].

Thus, the indication of this antiangiogenic drug in European countries is still a matter of debate, and further studies aiming at identifying which patients are more likely to benefit from this therapy are warranted. Prior to its assessment in patients with newly diagnosed glioblastoma, TTFields were first investigated at the recurrence setting. A phase III trial (NCT00379470) conducted on patients with recurrent disease compared treatment with alternating electric fields without chemotherapy vs. the best available chemotherapy according to the local physician’s choice. No

Figure 3
Sustained complete response in a 62 year-old female patient treated with Bevacizumab alone after second recurrence of glioblastoma with unmethylated MGMT promoter. A. Baseline MRI. B. MRI obtained 28 months after Bevacizumab initiation. MRI: magnetic resonance imaging.
improvement in OS was demonstrated (6.6 vs. 6.0 months). However, efficacy and activity with that chemotherapy-free treatment device appeared comparable to chemotherapy regimens commonly used in patients with recurrent glioblastoma. Moreover, toxicity and quality of life outcomes resulted more favourable in the group treated with TThFields compared with systemic chemotherapy [83].

Given the lack of a curative treatment and an effective standard of care at recurrence, this setting appears appropriate for rapid development of clinical trials. Whenever possible, clinicians should consider this option and encourage patients to participate in clinical trials investigating the potentially effective experimental therapies.

**Elderly patients**

Elderly patients, particularly those aged 70 years old or over, were traditionally excluded from participating in clinical trials, and thus no standard of care existed for this group of patients. Moreover, the unfounded presumption of an increased risk of toxicity and lack of efficacy precluded many of these patients from receiving active antitumor treatment, with therapeutic efforts reduced solely to supportive care [84].

However, the incidence of glioblastoma has significantly increased in the older segments of the population over the past decades, due in part to a demographic change with continuous aging of the society. In fact, patients aged 65 or more currently account for half of all patients suffering from this disease. These circumstances have led in the last 10 years to substantial efforts aimed at improving the management of this disease in older patients, taking into account not only survival outcomes but also cognition and quality of life issues [85].

Retrospective studies suggest that the elderly can undergo aggressive neurosurgery without increased surgical morbidity [86]. In addition, as previously mentioned, a small study conducted in Finland evaluated prospectively the effectiveness of craniotomy and tumor resection compared to stereotactic biopsy in a group of glioblastoma patients aged 65 years or older. Importantly, this study demonstrated a gain in survival and also quality of life in patients who underwent tumor resection compared to those in whom surgery consisted only in stereotactic biopsy (5.7 months vs. 2.8 months, respectively) [38]. The ANOCEF is currently conducting a phase III trial (CSA trial; NCT02892708) addressing the efficacy and safety of surgical resection in elderly patients aged 70 years or older with newly diagnosed supratentorial glioblastoma. Eligible patients, with KPS of 50% or higher, are randomly assigned to either surgical resection followed by focal radiotherapy or to purely diagnostic biopsy with further radiation therapy. The results of this large study will provide valuable highlights in the beneficial role of surgery in these patients.

In 2007, the French RSP phase III trial (NCT00430911) confirmed the benefit of radiotherapy in elderly patients with newly diagnosed glioblastoma and good performance status. In this multicentre study, 81 patients aged 70 years or older were randomized to receive palliative care alone or palliative care in addition to radiation therapy with a dose of 50 Gy at 1.8 Gy per once-daily fraction. This latter group of patients exhibited improved survival (3.9 months vs. 6.8 months) and, importantly, radiation therapy did not carry on a deterioration of quality of life, performance status nor cognitive functions [87]. On the basis of these results, radiotherapy became the standard of care for elderly patients with glioblastoma until very recently.

Another important randomized trial compared a conventional course of radiotherapy (60 Gy in 30 fractions over 6 weeks) with an abbreviated regimen (40 Gy in 15 fractions over 3 weeks) in 100 glioblastoma patients aged 60 years or older. No significant differences were found on survival times (5.1 months vs. 5.6 months). In addition, patients receiving the short-course radiotherapy were less likely to discontinue the treatment and required fewer increases in dosage of post-treatment corticotherapy [88]. This study and other non-controlled series suggested that hypofractionated radiotherapy was safe and feasible for elderly patients with glioblastoma [89].

Later on, considering possible toxicity and practical disadvantages linked to radiotherapy in advanced age patients, two large randomized phase III trials evaluated the role chemotherapy as a therapeutic alternative. The NOA-08 German trial (NCT01502241) included 373 patients aged 65 or older, and randomly compared a dose-dense regimen of temozolomide (100 mg/m²/day for 7 consecutive days every 14 days) with a conventional radiotherapy regimen of 60 Gy in 30 fractions over 6 weeks. No differences were found in survival times (8.6 months vs. 9.6 months, respectively), and patients whose tumor had MGMT promoter methylation benefited the most from alkylating chemotherapy [90]. Similarly, the three-armed Nordic Clinical Brain Tumor Study Group trial (SRCTN81470623) compared monotherapy with temozolomide (200 mg/m²/day for 5 days every 28 days) with two radiotherapy regimens, standard schedule of 60 Gy administered in 30 daily fractions over 6 weeks and a hypofractionated protocol of 34 Gy delivered in 10 sessions over 10 days. This study included 342 newly diagnosed glioblastoma patients with ages 60 years or over, and found an increased survival with temozolomide alone compared to standard radiotherapy (8.3 months vs. 6.0 months) while no differences were achieved between temozolomide and hypofractionated radiotherapy nor between both radiation schedules. Again, MGMT promoter methylation was associated with a longer survival among patients receiving temozolomide treatment [91].

The question whether transferring the combined radio-chemotherapy with temozolomide regimen to the elderly improves survival in such population has been recently answered by an international phase III trial (NCT00482677) conducted by the CCTG, EORTC and TROG. In this study, 562 newly diagnosed
glioblastoma patients aged 65 or over were randomly assigned to receive either radiotherapy alone (40 Gy administered in 15 fractions over 3 weeks) or the same radiotherapy schedule with concomitant (75 mg/m²/day) and up to 12 cycles of adjuvant temozolomide (150–200 mg/m²/day for consecutive 5 days every 28 days). Both OS and PFS were significantly longer with radiotherapy plus temozolomide than with radiotherapy alone (OS: 9.3 months vs. 7.6 months; PFS: 5.3 months vs. 3.9 months). Importantly, again combination treatment was well-tolerated in this elderly population and their survival advantages did not come at a cost to quality of life. Notably, although the survival benefit conferred by adding temozolomide to radiotherapy was greatest among patients with methylated MGMT promoter, all patients derived survival benefit from the combined therapy [92]. These results support consideration of this multimodal treatment as new standard of care for this aged population with newly diagnosed glioblastoma and good performance status, regardless of MGMT promoter methylation status.

However, the issue that arises now is whether a combined treatment with standard long-course (60 Gy in 30 fractions over 6 weeks) radiotherapy might add any benefit, and thus further trials addressing this issue are awaited.

**Patients with poor performance status**

In addition to extent of surgery and age, performance status constitutes a strong independent prognostic factor [93]. Around 30–40% of patients with newly diagnosed glioblastoma exhibit a poor performance status [94–96]. Precisely because of their associated poor prognosis, many of these patients are excluded from participating in clinical trials. As a consequence of this lack of evidence, the management of these patients remains very difficult and in fact many of them do not receive active antitumor treatment [97].

For young patients with impaired functional status but who can undergo radio-chemotherapy with temozolomide, addition of bevacizumab could have a positive impact on symptomatic and maybe also survival outcomes. And, for those young patients who are not suitable for receiving standard or abbreviated radiochemotherapy with temozolomide, upfront treatment with temozolomide alone or in association with bevacizumab might remain an option [97]. However, the role of these possible approaches still needs to be validated in specific prospective trials.

On the other hand, the management of elderly patients with poor functional status has been specifically assessed in two non-randomized phase II trials conducted in France [98,99]. These severely impaired patients with very short survival expectancy are less likely to undergo surgery, and radiotherapy appears too inconvenient for them also. In this context, chemotherapy with temozolomide appears to be an acceptable alternative. The ANOCEF TAG trial (NCT01242566) evaluated precisely the efficacy and safety of temozolomide (150–200 mg/m² for 5 consecutive days every 28 days) in this population. Seventy patients aged 70 years old or older and with a Karnofsky Performance Score equal or inferior to 60% were included in the study. One fourth of the patients achieved a radiological response, and the observed median overall survival of 25 weeks clearly exceeded the 12-week survival expected for similar patients treated only with best supportive care. Interestingly, one third of the patients had an improvement in functional status, the majority of them becoming able of self-caring for a period of time ranging from 1 to 9 months. Consistently with the literature, in general patients with methylated MGMT promoter benefited the most from this treatment. Importantly, treatment with temozolomide was well tolerated, with hematologic and non-hematologic toxicities similar to that observed in younger patients with preserved functional status [98].

Hereinafter, another ANOCEF non-randomized phase II trial (NCT02898012) evaluated the role of adding bevacizumab (10 mg/kg every 14 days) to upfront temozolomide in the same population of elderly glioblastoma patients with poor performance status. Sixty-six patients were included, and survival and functional outcomes appeared not different from those obtained in the abovementioned TAG trial, confirming the utility of temozolomide in this specific population and suggesting that the addition of the antiangiogenic agent might not confer additional benefit [99].

**Conclusion**

In conclusion, diffuse gliomas constitute a diverse group of malignant tumors with varying aggressive course and heterogeneous survival. In general, the mainstay of treatment of these distinct tumors is still based on the combination of surgery and other classical therapeutic weapons such radiotherapy and chemotherapy. Important clinical trials investigating these modalities have led to meaningful improvement in survival times over the past decades. In addition, recent advances in molecular profiling have allowed the identification of patients with better prognosis and more likely to respond, at least transiently, to specific antitumor treatment. This is particularly true for grade II and III 1p/19q-codeleted gliomas, a subset of tumors in which data maturation after long-term follow-up have proved extremely important for accurate assessment of efficacy. However, relevant questions regarding the optimal management of specific patient populations are still unsolved. In this context, further prospective studies should address the best sequence of surgery, radiotherapy and chemotherapy in good prognostic diffuse low-grade glioma patients, or the most convenient treatment for grade II and III infiltrating gliomas without IDH mutations. Also, whether temozolomide is comparable to PCV chemotherapy in terms of efficacy is another issue that still remains unanswered, as well as the optimal management of glioblastoma patients with poor performance status and the
most appropriate radio-chemotherapy protocol for elderly glioblastoma patients. Studies addressing these issues will provide useful answers to these topics and will thus improve the pattern of care of these patients. Despite early unpromising results, novel targeted therapies and diverse immunotherapy strategies are still focus of current research. Because there is no cure for diffuse gliomas yet, active research into the development of novel therapies is warranted.

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Management of diffuse glioma


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