Brain Gliomas in the Elderly

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8.1 Introduction

Adult's gliomas are a group of primary central nervous system (CNS) neoplasms arising from neuroglial cells. In the World Health Organization, they are classified according to their phenotype and to a histological grading system. The grade I corresponds to pilocytic astrocytoma. The grade II corresponds to low-grade diffuse astrocytoma, oligodendroglioma and oligoastrocytoma. High-grade gliomas comprise anaplastic astrocytoma, anaplastic oligodendroglioma (grade III) and glioblastoma multiforme (GBM), which is the most frequent and most aggressive subtype (grade IV) [38]. However, this broad grouping contains tumours that are clinically, histologically and molecularly heterogeneous.

Low-grade gliomas are more common in young adults, while anaplastic gliomas and GBM occur more frequently in older patients [48]. Due to the global increase in life expectancy, the incidence of gliomas in elderly patients, especially GBM, is increasing [36]. The cut-off to define elderly patients with gliomas varies across studies between 65 and 70 years old [54].

Due to their frequently very poor prognosis and the fear that they may not tolerate brain radiotherapy (RT) and chemotherapy, elderly patients with gliomas have long been undertreated. However, within the last decade, several clinical trials conducted in this specific population have resulted in significant progress. This chapter attempts to summarize the main clinical, diagnostic and treatment features of brain gliomas in the elderly population.

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8.2 High-Grade Gliomas

8.2.1 Glioblastoma Multiforme

8.2.1.1 Epidemiology

Glioblastoma multiforme (GBM) is the most frequent malignant primary brain tumour in adults (46 %). Patients older than 65 years old represent nearly 50 % of all patients [48]. The definition of elderly patients with GBM varies, but in general a cut-off of 65 or 70 years old is well accepted. The median overall survival (OS) of elderly patients with GBM ranges from 4 to 8.6 months [26]. The incidence of elderly patients with GBM is increasing. Hence, elderly people represent an important part of the total number of newly diagnosed GBM, and consequently these patients need to be considerated when new treatment approaches are developed [17].

8.2.1.2 Clinical Features

In elderly patients, focal neurological deficits (55 %) and cognitive impairment (48.5 %) are the most common symptoms at diagnosis [84]. Elderly patients present less likely with headache or seizures when compared to young patients. Since the onset of symptoms frequently occurs over a few weeks, it is important to perform a rapid diagnosis in order to start treatment before the performance status is too deteriorated [17, 39].

8.2.1.3 Prognostic Factors

Different prognostic factors have been evaluated in elderly patients with GBM [4]. Even in this population, an older age is associated with a poorer outcome [13]. As in younger patients, the Karnofsky Performance Status (KPS), with a cut-off at 70, or ECOG PS ≤ 2 has been shown to be associated with a poorer outcome [2, 55, 84]. Other prognostic factors include gross total resection [68] and *MGMT* promoter methylation status [16, 25]. Mutation of isocitrate dehydrogenase 1 (IDH1) has been identified in around 10 % of adult patients with GBM, and its positive impact on clinical outcome has also been demonstrated [6, 81]. The IDH1 mutation is less frequently reported in the geriatric population (1–2 %) which may partly explain the worse prognosis of those patients [24, 79]. The lack of other favourable prognostic biomarkers in elderly patients such as G34R H3F3A mutation, a G-CIMP, or PRDX1 methylation may also contribute to the overall worse outcome [79].

8.2.1.4 Radiology

On brain magnetic resonance imaging (MRI), GBMs typically present as large masses located in the supratentorial area. A hypo- or isointense lesion on T1 sequences with a central heterogeneous signal related to necrosis is usually observed. Sometimes, intratumoural bleeding is also present. T1 sequences after contrast administration frequently show thick and irregular ringlike contrast enhancement. Noteworthy, approximately one third of patients can present with lack of contrast enhancement, especially in elderly patients [61]. On FLAIR sequences, the tumour generally appears as a hyperintense mass surrounded by vasogenic fingerlike

oedema. Multimodal MRI including diffusion, perfusion and MRI spectroscopy can help better characterize the tumour. MR spectroscopy provides information about metabolic tissue composition. The most useful metabolites in the diagnosis of GBM are choline which is related with membrane turnover, creatine reflecting basal metabolism, **N-**acetyl-aspartate (NAA) related to neuronal structures and lipids or lactate, both reflecting necrosis. MRI spectroscopy typically shows lactate or lipid peaks with an increased choline/NAA ratio. Perfusion MRI typically shows an elevated rCBV suggestive of neo-angiogenesis with higher values in geriatric population when compared to younger population [27, 29]. The differential diagnosis in this setting includes a unique brain metastasis and a pyogenic abscess, toxoplasmosis in HIV patients and tuberculoma in patients living in regions where tuberculosis is endemic [47]. Primary CNS lymphoma is rarely necrotic. In addition to a complete clinical exam, elderly patients with a suspicion of GBM should undergo thoracic-abdominal CT scan. Diffusion MRI should be carefully reviewed to exclude a pyogenic abscess which is frequently present without fever and any biological sign of inflammation. HIV serology should be systematic.

8.2.1.5 Treatment

Surgery

Surgery or biopsy is first required to obtain a definitive diagnosis. Even though MRI is frequently suggestive of the diagnosis, histology remains mandatory to exclude differential diagnosis. In addition, tumour tissue is needed for molecular analysis since molecular profiling is playing an increasing role in treatment decisions.

In younger patients, maximal safe surgical resection of the GBM is recommended. This recommendation however does not rely on randomized studies but on retrospective analysis of several clinical trials showing that in younger adults, a maximum safe resection is associated with a better OS independently of other prognostic factors [1, 65].

The role of surgery in elderly GBM patients remains debated. A retrospective analysis on the management of GBM in Spain between 2008 and 2010 showed that patients older than 70 years old presented a higher incidence of complications after surgery compared to their younger counterparts (12.6 % vs 18.8 %) and were less likely to undergo resection [22]. Another analysis of the perioperative complications in elderly population found similar results with an increased incidence of hematomas in the cavity and pneumonia [2]. On the other hand, some retrospectives studies support that elderly patients should be treated with a surgery as they present a better outcome with no increase of surgery-related morbidity [12, 49]. Yet a retrospective study of 289 patients concluded that despite maximum tumour resection should be attempted, surgery may be less useful in patients older than 80 years with a KPS less than 80 % [34]. Advances in intraoperative techniques have helped to maximize tumour resection and minimize morbidity in gliomas' surgeries. Awake craniotomy and the use of 5-aminolevulinic allow to perform more complete resections and also reduce the risk of postoperative deficits [41, 68]. A retrospective analysis suggested a benefit on survival of awake craniotomy in elderly population

without increasing postoperative morbidities [23]. However, the value of these techniques in the geriatric population remains to be studied.

One prospective randomized trial compared resection versus biopsy in 30 elderly patients (median age was 70 years old) with newly diagnosed high-grade gliomas [75]. In this study, surgery was associated with longer survival compared to biopsy (171 days versus 85 days, respectively) and was also related with an improvement of the quality of life. Nevertheless, this study was limited by its small sample size and the inclusion of both GBM and anaplastic astrocytomas. The ANOCEF group (the French specialized association of neuro-oncology) has undertaken a randomized phase III study comparing surgery versus biopsy in elderly patients with GBM.

Initial Treatment in Patients with Good Performance Status

Radiotherapy

In young patients (<70 years old) with good KPS, since 2005, the standard of care for newly diagnosed GBM is maximal safe surgical resection followed by concomitant and adjuvant temozolomide radiochemotherapy (TMZ-RT) [70]. In patients aged <70 years, compared to RT alone, TMZ-RT was associated with increased median survival (12.1 vs 14.6 months) and an increase of the rate of patients alive at 2 and 3 years (27.2 % and 16 %, respectively) without important toxicity [69].

In elderly GBM patients, even in those with good KPS, whether oncological treatment might be beneficial has long remained debated. Keime-Guibert et al. conducted the first randomized trial in this population. This trial compared, in 85 patients aged ≥70 years and with a KPS ≥70, RT only (50.4 Gy, 28 fractions) versus best supportive care. Thirty-nine patients received RT and 42 patients received supportive care. The study was closed prematurely because the preliminary analysis showed clearly an increase in the OS of patients included in the RT arm (29 weeks versus 17 weeks ($p = 0.002$). Importantly, RT was well tolerated and was not associated with a decrease of the performance status, the quality of life or the cognitive function [33]. While in Keime-Guibert et al. study patients received a RT regimen close to that administered in LGG patients, several studies aimed at determining the optimal RT regimen in elderly patients. In 2004, a randomized trial compared an accelerated RT regimen (40 Gy, 15 fractions during 3 weeks) to a standard irradiation schedule (60 Gy in 30 fractions) in patients aged 60 years or more and showed no differences regarding median OS (5.6 and 5.1 months, respectively) and the KPS at the end of the treatment. However, patients treated with the classical schedule required more frequently an increase in the corticosteroid dose (49 % versus 23 %) suggesting a worse tolerance of the conventional dose [56]. Recently, a phase III randomized trial randomized elderly or frail patients to receive an even more accelerated hypofractionated regimen (25 Gy in five daily fractions over 1 week) or the most commonly schedule of RT used in elderly population (40 Gy in 15 daily fractions over 3 weeks). No differences in OS or survival (PFS) were identified [57].

Temozolomide

Besides RT, several retrospective studies suggested that TMZ could be an effective treatment in elderly GBM patients [21, 35], and this hypothesis was tested in two randomized phase 3 trials. Wick et al. conducted a non-inferiority phase III trial (NOA-08 study) where they compared TMZ vs RT in patients aged over 65 years old with a KPS ≥60 with a high-grade glioma. The patients were randomly assigned to receive either a dose-intensified TMZ regimen (100 mg/m^2/day days 1–7 of 1 week on, 1 week off) or standard RT (60 Gy over 6 weeks in 1.8–2 Gy fractions). No significant difference was found in terms of OS (8.6 months for the TMZ arm and 9.6 months for the RT arm), and no difference was identified in both groups regarding quality of life [78].

The second study, the Nordic trial, was conducted by Malmström et al. They enrolled 342 patients aged 60 years or older with a diagnosed GBM. Patients were randomized to receive one of the following three treatment arms: (a) TMZ (200 mg/m^2 for 5 consecutive days every 28 days), (b) hypofractionated RT (34 Gy in 10 fractions) and (c) standard schedule of RT (60Gy/30fractions). In the whole population, OS was significantly better in patients treated with TMZ than with the standard RT regimen (8.3 versus 6 months, $p = 0.01$). In patients aged ≥70 years, TMZ and accelerated RT were equivalent and were superior to the standard RT regimen (OS 8.4 versus 7.4 months) [40]. At 3 months, TMZ was associated with a better quality of life than RT. Yet no subsequent analysis of quality of life was performed, and therefore these results need to be taken with caution. An example of good response to treatment with TMZ in an elderly patient is shown in Fig. 8.1.

MGMT Promoter Methylation

Interestingly, a retrospective analysis of *MGMT* methylation was performed in these two phase III trials, the NOA-8 and the Nordic trial [40, 78]. *MGMT* methylation was analysed in 56 and 69 % of patients in the NOA-8 and in the Nordic trial, respectively. In the NOA-8 trial (patients ≥65 years), *MGMT*-methylated patients had a longer PFS when treated with TMZ as opposed to RT (8.4 vs 4.6 months, $p = 0.01$), while *MGMT* unmethylated patients had a longer PFS when treated with RT than with TMZ (4.6 vs 3.3 months, $p = 0.01$). A similar yet not significant trend was observed for OS. The Nordic trial (patients ≥ 60 years) showed a non-significant trend towards longer OS in *MGMT*-methylated patients when treated with TMZ rather than with RT (hazard ratio = 0.64, $p = 0.07$), but *MGMT*-unmethylated patients did not fare better when treated with RT than with TMZ. PFS data were not available for this trial, as these data were deliberately not collected. These results, together with another retrospective study, suggest that *MGMT* methylation could guide treatment decision in elderly patients with glioblastoma [79]. However, the data are not yet robust enough to be translated into the clinic and need prospective validation. Until now, the use of *MGMT* methylation as a predictive factor has also been limited by the fact that the optimal technique to study *MGMT* methylation is still debated. In Quillien et al., the rate of *MGMT* methylated patients varied from

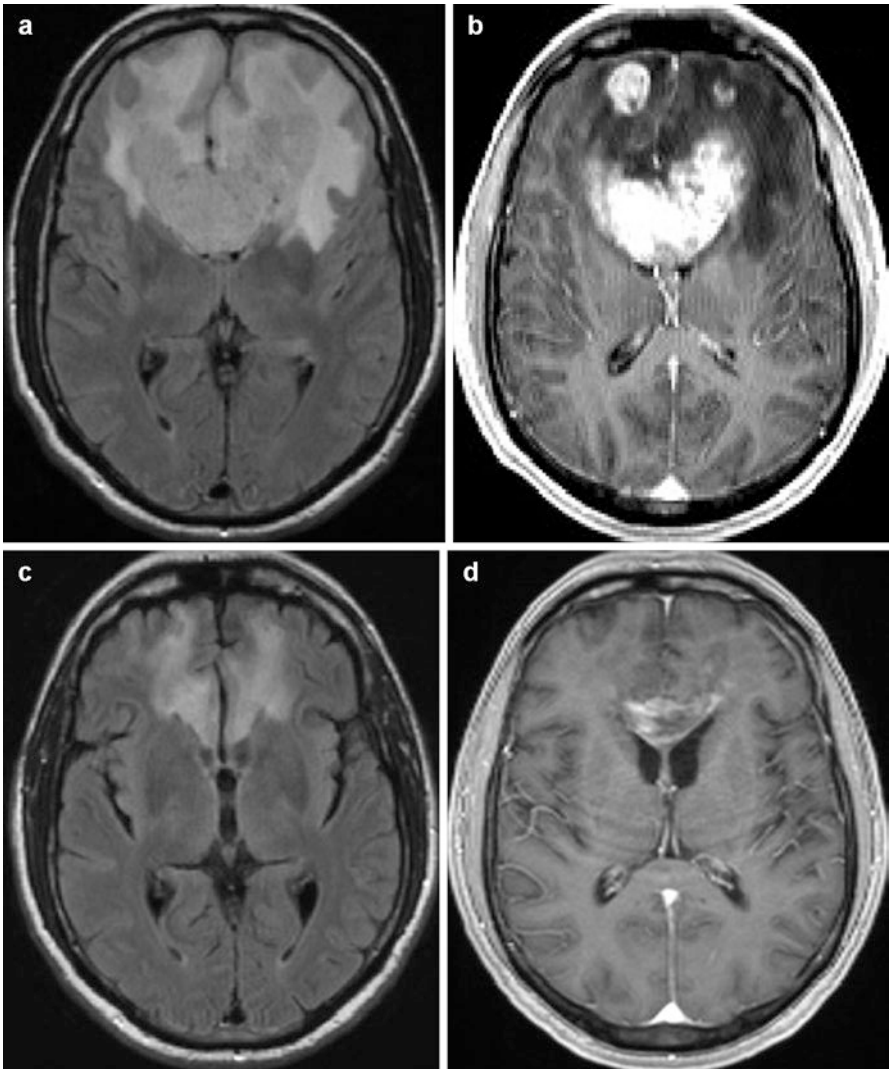

Fig. 8.1 (**a**, **b**) Magnetic resonance image (MRI) of an elderly male patient (71 years old) with newly diagnosed glioblastoma multiforme (GBM). Flair sequence shows a large and oedematous hyperintense lesion infiltrating both frontal lobes and corpus callosum (**a**). T1-weighted axial gadolinium-enhanced MRI showing two contrast enhancing lesions in the setting of a multicentric GBM (**b**). (**c**, **d**) Follow-up MRI from the same patient after six cycles of treatment with temozolomide. Flair sequence shows a marked reduction of the oedema (**c**). Dramatic improvement of the contrast enhancement lesions is observed after the administration of gadolinium (**d**). The patient presented a neurological improvement and the KPS increased from 50 to 70 %. The overall survival was 18 months

33 to 60 % depending on the method that was used [53]. Methylation-specific PCR has been used as a standard to study *MGMT* methylation, but this method is only qualitative and lacks automation. Therefore, alternative semi-quantitative and

quantitative techniques have been developed. However, these techniques do not study exactly the same regions of the *MGMT* promoter. Therefore, as the methylation pattern of the promoter can be heterogeneous, some patients are classified as methylated or as unmethylated depending on the technique used [53].

Radiotherapy and Temozolomide

Since temozolomide radiochemotherapy has improved the prognosis of younger patients with GBM, an important question until recently was whether this strategy may be beneficial in elderly patients and may not be too neurotoxic. Some non-randomized prospective studies had suggested the possible benefit of radiochemotherapy in elderly population [31, 44, 45]. This was also supported by a meta-analysis based on non-randomized studies comparing both therapeutic options (RT with TMZ versus RT alone) [82]. Finally the benefit of this strategy was recently proven by the results of the collaborative CCTG CE.6/EORTC 26062-22061/TROG 08.02/NCT00482677 trial which were presented at the 2016 ASCO meeting [50]. This trial compared RT alone (40 Gy in 15 fractions) vs RT/TMZ (40 Gy in 15 fractions associated with concomitant TMZ followed by up to 12 monthly TMZ cycles). Five hundred sixty-two patients were randomized, 281 on each arm; median age was 73 years, 77 % of patients had a KPS > 70 and 68 % had a resection. RT/TMZ significantly improved OS over RT alone (median 9.3 months vs 7.6 months, $p < 0.0001$) and significantly improved PFS (median 5.3 months vs 3.9 months, $p < 0.0001$). Preliminary *MGMT* analysis demonstrated a clear benefit of RT/TMZ vs RT alone in *MGMT* methylated patients (13.5 months vs 7.3 months, $p = 0.0001$) but also in *MGMT* unmethylated patients, however to a lesser extent (10 months vs 7.9 months, $p = 0.055$). Quality of life analyses showed no differences in functional domains of QLQC30 and BN20 but were worse in the RT/TMZ arm for nausea, vomiting and constipation. The authors concluded that the addition of concomitant and adjuvant TMZ to hypofractionated RT for elderly patients with GBM significantly improved OS and PFS in all patients and that it was well tolerated.

Initial Treatment in Patients with Poor KPS

The cut-off to define low KPS can vary in some reports but equal or less than 60 is well accepted. The optimal management of young patients with poor performance status is based mainly on retrospective studies and a subgroup analysis of prospective studies [14, 42]. A maximal safe resection is highly recommended when possible especially if it can improve the neurological status. Concerning the postsurgical treatment, it remains debated in the absence of prospective studies. Some patients may benefit from adding bevacizumab to TMZ radiochemotherapy [18].

In elderly patients with poor performance status, supportive care is frequently a reasonable option. However, in some patients, TMZ chemotherapy may be an alternative. The French ANOCEF group performed a phase II non-randomized trial in this population [19]. Seventy patients older than 70 years old with poor KPS and a newly diagnosed GBM received TMZ (150–200 mg/m^2/day, 5 days every 28 days). Median PFS and OS were 3.5 and 5.5 months, respectively, comparing favourably with historic controls only treated with supportive care. It is of note that 33 % of patients presented an improvement in their KPS by 10 or more points and that

overall quality of life and cognition improved over time. In addition, *MGMT* promoter methylation was associated with longer survival even though only 44 % of patients could be analysed. Treatment was generally well tolerated with toxicity rates similar to those observed in young patients with good performance status [19]. More recently, the ANOCEF group conducted a prospective phase II non-randomized trial in the same population to evaluate the benefit of adding bevacizumab to TMZ. This study confirmed the benefit of TMZ, yet the addition of bevacizumab did not seem to confer additional benefit [20].

Recurrent Glioblastoma Multiforme

In young patients with glioblastoma, there is no standard of care at recurrence. Treatment options include re-surgery, re-challenge with TMZ, bevacizumab and nitrosoureas. Yet inclusion of patients in clinical trials is highly recommended.

Currently, there is no evidence for re-irradiation, and cognition toxicity is a limitation factor. Different studies showed controversies regarding the benefit of re-surgery in patients with poor performance status [43, 80]. However, a new tumour sample can be of utility in order to confirm the diagnosis, rule out a possible radionecrosis or perform molecular analysis.

Concerning chemotherapy, TMZ is one potential option at the recurrence in patients who present *MGMT* methylation [7, 83] and firstly presented a good response. However, the best schedule of TMZ at the recurrence is not well defined [76]. Nitrosoureas (carmustine, lomustine, fotemustine) have been a classical treatment in GBM recurrences, and several reports describe their benefit [8, 60] despite their haematological toxicity. Bevacizumab in monotherapy presents a clinical activity; however, its impact on survival is not clear. Furthermore, the combination with nitrosoureas improves the PFS despite their benefit on OS has not yet been confirmed [71]. In addition, many new target agents have emerged, but their efficacy remains to be confirmed [63].

In elderly patients with GBM, as in younger patients, there is no standard of care. All cases should be discussed on multi-disciplinary meetings, and the decisions should be based on the performance status. The main options are RT or preferably chemotherapy with TMZ or bevacizumab because of their relative safety side effect profile. Re-surgery or re-irradiation is not a feasible option in this fragile population. When performance status is not optimal, supportive care should be considered as a first option.

8.2.1.6 Conclusion

The management of elderly patients with GBM has evolved over the time, and several treatment options have emerged in the last few years. As an example, in Lyon, the median survival of elderly patients with GBM increased from 3 to 6 months between 2004 and 2008 [5]. However, the best therapy should be selected considering the functional status of the patient. Regarding the controversy of maximal safe resection versus biopsy, some retrospectives studies and one prospective study support that resection of the tumour should be done when feasible. The optimal treatment after surgery or biopsy in patients with good performance status is accelerated

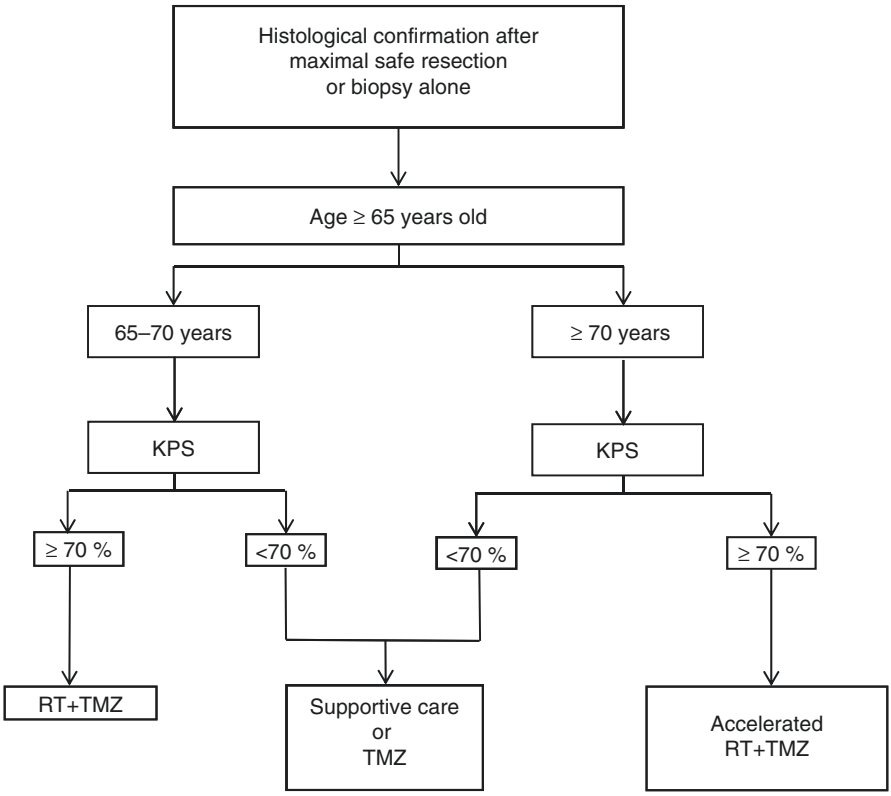

Fig. 8.2 Algorithm of treatment in newly diagnosed glioblastoma multiforme in elderly patients. *KPS* Karnofsky performance status, *RT* radiotherapy, *TMZ* temozolomide

RT/TMZ as recently shown in a large phase III trial. In some patients with poor performance status, TMZ may be an alternative to palliative care, especially in patients with a methylated *MGMT* promoter. However, the predictive impact of *MGMT* promoter methylation status in elderly patients still needs confirmation in prospective trials. An algorithm of treatment in these patients is proposed on Fig. 8.2. A summary of the main treatment studies in newly diagnosed GBM in the elderly population is also added (Table 8.1).

8.2.2 Anaplastic Gliomas

The exact incidence of anaplastic gliomas in elderly patients remains to be determined; however, they seem rare [48]. In young patients, anaplastic gliomas form a heterogeneous group of gliomas in terms of clinical, histological and molecular profiles. The survival times of patients range from a few years to more than 15 years [11]. This clinical heterogeneity reflects underlying molecular heterogeneity. From a

Table 8.1 Main studies of treatment in elderly patients with glioblastoma multiforme

Authors (Year)	Study design	Treatment	*N*	Age (years)	Median age (years)	KPS (%)	Median OS (months)	Median PFS (months)
Roa et al. [56]	Phase III	Standard RT[a] HypoRT[b]	47 48	≥60	72	≥50	5.1 5.6	NA NA
Keime-Guibert et al. [33]	Phase III	RT[c] SC	39 42	≥70	73	≥70	7.3 4.2	3.75 1.25
Gallego Perez-Larraya et al. [19]	Phase II	TMZ[d]	70	≥70	77	<70	6.25	4
Malmstrom et al. [40]	Phase III	HypoRT[e] TMZ[f] Standard RT[a]	98 93 100	≥65	70	≥60	7.5 8.3 6	NA NA NA
Wick et al. [78]	Phase III	TMZ[g] RT[a]	195 178	≥65	72	≥60	8.6 9.6	3.3 4.7
Roa et al. [57]	Phase III	HypoRT[b] Short-course RT[h]	50 48	≥50	NA	≥50	6.4 7.9	4.2 4.2
Perry et al. [50]	Phase III	HypoRT + TMZ[i] HypoRT[b]	281 281	≥65	73	≥70	9.3 7.6	5.3 3.9

RT radiotherapy, *NA* not available, *HypoRT* hypofractionated radiotherapy, *SC* supportive care, *TMZ* temozolomide

[a]60Gy/30fractions/6 weeks

[b]40Gy/15fractions/3weeks

[c]50Gy/28fractions/5–6weeks

[d]150–200 mg/m^2 per day for 5 days

[e]34Gy/10fractions/2weeks

[f]200mg/m^{2}per day for 5 days

[g]100mg/m^2 per day, for days 1–7 and 15–21

[h]26Gy/5fractions/1week

[i]40Gy/15fractions/weeks plus concomitant TMZ followed by monthly adjuvant TMZ until progression or 12 cycles

molecular point of view, three main subgroups can be distinguished based on two biomarkers, the 1p/19q co-deletion and the isocitrate dehydrogenase (IDH) mutation status. Gliomas with the 1p/19q co-deletion (which are virtually all IDH mutated) display the best prognosis [9]. The IDH-mutated gliomas, without 1p/19q co-deletion, have an intermediate prognosis. Finally, the non-1p/19q co-deleted and non-IDH-mutated gliomas have a poor prognosis. In younger patients, two randomized phase III studies have demonstrated that IDH-mutated patients (with or without 1p/19q co-deletion) benefit from adjuvant PCV chemotherapy in addition to RT which is not the case of patients without IDH mutation [10, 11, 74]. These patients have a prognosis close to that of GBM patients and are treated with TMZ radiochemotherapy.

In elderly patients, no prospective study has focused on anaplastic gliomas, and the rare retrospective studies in this population did not stratify patients according to the 1p/19q co-deletion and the IDH mutation [67]. IDH wild-type anaplastic gliomas in elderly patients should probably be treated like GBM patients. IDH-mutated anaplastic gliomas without 1p/19q co-deletion should probably receive RT plus adjuvant TMZ instead of PCV chemotherapy given (i) the potential toxicity of this regimen in patients over >70 years and (ii) the fact that TMZ may be equally effective as PCV even if this has not been formally demonstrated. In elderly patients with a 1p/19q co-deleted anaplastic glioma, chemotherapy only with TMZ may be

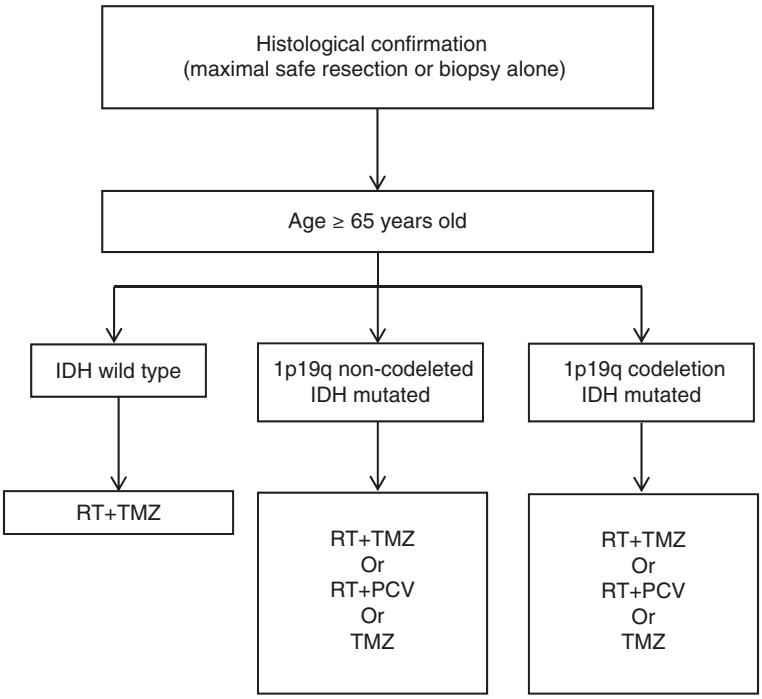

Fig. 8.3 Algorithm of treatment in newly diagnosed anaplastic gliomas in elderly patients. *IDH* isocitrate dehydrogenase, *RT* radiotherapy, *TMZ* temozolomide, *PCV* procarbazine, lomustine and vincristine

considered since these tumours are usually very chemosensitive [67]. A therapeutic algorithm is proposed on Fig. 8.3.

8.3 Low-Grade Gliomas

8.3.1 Epidemiology

LGG represent 15 % of all brain tumours in adults; the peak incidence occurs in people between 35 and 44 years old [51, 52]; nevertheless, nearly 8 % of LGG occur in patients of 60 years old [32]. However, this incidence may be underestimated because old patients are less likely to undergo surgery preventing histological confirmation of the diagnosis. The median OS in this population is shorter than in young population being around 3 years with a 5-year survival rate of 40 % [32, 52, 62].

8.3.2 Clinical Features and Prognostic Factors

Clinical manifestations in older population differ from their younger counterparts. A retrospective study identified that elderly patients presented more frequently with a clinical deficit (53 % of patients presented sensory or motor disturbances, language disorders, cognitive impairment), whereas epilepsy was the most common symptom in young patients (80 % of patients) [32, 51]. In young patients, age over 40 years old, preoperative neurological deficit, large tumours, tumour crossing midline and astrocytoma histology are associated related in LGG. In young patients with newly diagnosed LGG, age over 40 years old, preoperative neurological deficit, large tumour, tumour crossing midline and astrocytoma histology are pronostic factors for survival [51]. 1p/19q co-deletion and IDH mutation are also independent favourable prognostic factors. In older patients, astrocytic phenotype, increasing age and tumour crossing the midline were also negative prognostic factors [32].

8.3.3 Diagnosis

Magnetic resonance imaging (MRI) is the modality of choice for characterizing gliomas. These lesions are usually iso- or hypointense on T1 sequences and usually are confined to the white matter. T2 or FLAIR sequences show a hyperintensity lesion with a better delimitation of the lesion. They are commonly localized in supratentorial areas [52]. Contrast enhancement (CE) can be observed in up to 15 % of adults with LGG and is even more frequent in elderly population (44 %). However, it is mandatory to rule out an anaplastic glioma when CE is found. Furthermore, when a LGG is suspected in elderly population and despite the absence of CE, high-grade gliomas should be dismissed. Perfusion weighted imaging (PWI) may be an interesting tool in this setting [3, 37]. Conditions that may mimic an LGG in elderly patients are mostly stroke and

pseudotumoural presentation of cerebral amyloid angiopathy-related inflammation. In most cases (85%), this condition occurs in patients older than 60 years old presenting with cognitive impairment or focal deficits. The MRI demonstrates infiltrative white matter lesions with loco-regional mass effect, without contrast enhancement in most of cases and multiple microbleeds. Therefore, T2* sequences should be performed in elderly patients with a suspicion of LGG to rule out pseudotumoural presentation of cerebral amyloid angiopathy-related inflammation [58].

8.3.4 Treatment

8.3.4.1 Wait and See

Conservative management in young adults with LGG is characterized by a "wait and see" (WS) policy which consist in neuroimaging and clinical observation of those lesions that suggest LGG. Moreover, there is no evidence that early post-operative treatment is associated with improved survival [73]. Some authors suggest that for young patients with indolent LGG, the confirmation through stereotactic biopsy does not change the treatment; therefore, WS should be recommended [77]. When the lesion is surgically inaccessible or if the patients' symptoms are well controlled, WS could also be proposed. However, with this approach, there is a risk of tumour size increase.

In elderly patients, when an LGG lesion is suspected and the patient is practically asymptomatic, WS might be proposed as these tumours may have a very slow evolution.

8.3.4.2 Surgery

The surgery management of adults with LGG is controversial due to the lack of non-controlled studies. However, maximal safe resection is generally recommended in young patients.

Two recent large retrospectives studies in highly specialized centres support the benefit of early resection in the outcome of LGG and also highlight the minimal morbidity associated with surgery [30, 66]. There is evidence that awake craniotomy allows to perform more extensive safe resections [15, 59]. Noteworthy, histopathological diagnosis inconsistencies between surgery and biopsy have already been demonstrated, most especially in mixed gliomas with a low proliferation index [28, 46].

In elderly patients, there is no consensus on the optimal surgery management. Despite it is common to offer them biopsy or surgery without awake craniotomy, a recent report did not find significant differences in terms of perioperative mortality and morbidity when compared to young patients [23].

8.3.4.3 Radiotherapy

In adults, the role of adjuvant RT was investigated in the EORTC 22845 study, which compared early versus delayed RT. No differences between both groups in terms of OS were identified; however, PFS was higher in those patients firstly

treated with RT at the expense of side effects [73]. Therefore, if the patient does not present risk factors, delay RT until progression is recommended.

In geriatric population, RT is one suitable treatment option. However, as neurotoxicity of RT increases with age, it would be recommendable to optimize the dose to minimize the incidence of side effects.

8.3.4.4 Chemo-Radiotherapy Treatment

In adult LGG patients, two randomized studies have addressed the question of the optimal treatment in patients who need another treatment than surgery: the RTOG 9802 and the EORTC 22033–26033 trials [64, 72]. Shaw et al. compared in the RTOG 9802 trial RT to RT with PCV. First results did not show any benefit on OS with the combined treatment despite an increase of PFS was identified. However, a further long-term follow-up concluded that patients with less than a gross total resection and older than 40 years presented a better outcome after treatment with PCV and RT [64, 72]. Nevertheless, information about the benefit on OS in LGG stratified by their molecular profile and histological type has not been yet provided. The EORTC 22033–26033 trial conducted by Baumert et al. was designed for patients with a bad prognostic profile in order to investigate the impact of temozolomide chemotherapy or RT on PFS and OS. No statistically significant difference between both treatments was observed for PFS, and OS was not reached. However, first molecular analyses showed that non-1p/19q co-deleted patients presented similar outcome when treated with RT or TMZ, while non-co-deleted patients presented better responses when treated with RT [72]. Survival analyses will require further maturation as well as more detailed molecular analyses. Based on the results of these two studies, RT plus PCV should be considered the standard of care for LGG who require postsurgical adjuvant treatment.

The best therapeutic option in elderly population with LGG who require another treatment than surgery is not defined. No prospective study has been performed. Based on the trials above commented, RT plus chemotherapy could be recommended for patients who conserve a good performance status. For those patients with lower KPS, especially if they present with a 1p/19q co-deleted glioma, TMZ chemotherapy could be a more interesting option because of its safety profile.

8.3.5 Conclusions

LGG in elderly patients are less frequent and present a worst outcome compared to younger patients. The clinical presentation and the radiological features also differ from the presentation in the young population. In patients with slowly progressive LGG who are asymptomatic or have been operated, WS and follow-up might be the best option. In symptomatic patients who require a treatment, it should be selected based on KPS and molecular profile. Figure 8.4 shows an algorithm of treatment in elderly population with LGG diagnosis.

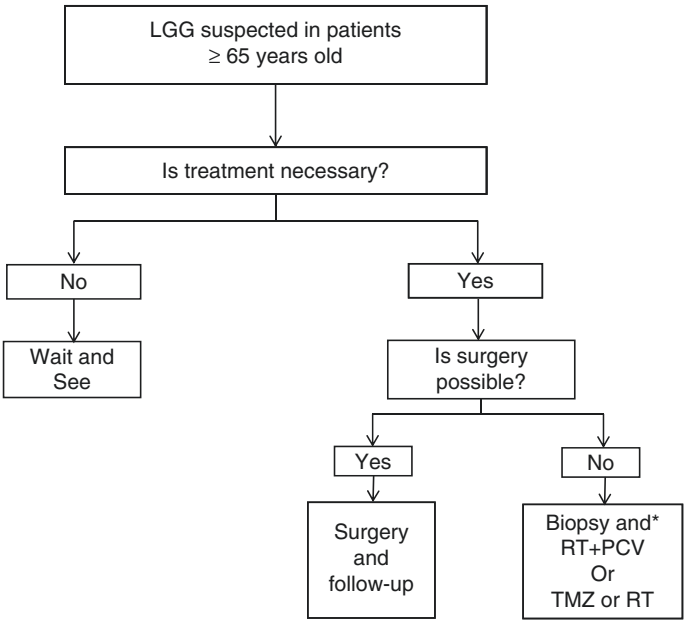

Fig. 8.4 Algorithm of treatment in newly diagnosed low-grade gliomas in elderly patients. *RT* radiotherapy, *TMZ* temozolomide, *PCV* Procarbazine, CCNU and Vincristine. *Patients should be treated acccording to their perfomance status and their molecular profile

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