Treatment of glioblastoma in elderly patients: an overview of current treatments and future perspective

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ABSTRACT

Current treatment of glioblastoma in the elderly includes surgery, radiotherapy and chemotherapy, but its optimal management is still debated. Longer survival after extensive resection compared with biopsy only has been reported, although the survival advantage remains modest. Radiation in the form of standard (60 Gy in 30 fractions over 6 weeks) and abbreviated courses of radiotherapy (30-50 Gy in 6-20 fractions over 2-4 weeks) has been employed in elderly patients with glioblastoma, showing survival benefits compared with supportive care alone. Temozolomide is an alkylating agent recently employed in older patients with newly diagnosed glioblastoma. The addition of concomitant and/or adjuvant chemotherapy with temozolomide to radiotherapy, which is currently the standard treatment in adults with glioblastoma, is emerging as an effective therapeutic option for older patients with favorable prognostic factors. The potential benefits on survival, improvement in quality of life and toxicity of different schedules of radiotherapy plus temozolomide need to be addressed in future randomized studies. Free full text available at www.tumorionline.it

Introduction

Approximately 176,000 cases of central nervous system (CNS) cancer are diagnosed per year worldwide, with an estimated annual mortality of 128,000¹. In the United States, 41,000 brain tumors are diagnosed annually, accounting for 1.35% of all cancers and 2.3% of all cancer-related deaths². The most common histologic type of primary brain tumors in the elderly is represented by glioblastoma multiforme (GBM), and its incidence is increasing especially in the elderly. The risk to develop a GBM rises with age, with an incidence rate among the elderly (more than 70 years old) of 17.5 per 100,000 person-years and a relative risk of 3-4 times compared with young adults³⁻⁴. Thus, the management of GBM in this population subgroup represents an important aspect of public health.

Current treatment of GBM in the elderly includes surgery, radiotherapy and chemotherapy, but its optimal management is still debated. Aggressive treatment may be inappropriate for older patients, and it is not clear whether the morbidity associated with surgery followed by chemoirradiation, as for young adults with GBM, outweighs the possible survival benefit in this population, leading many physicians to choose less aggressive treatment. Several studies have found that surgical resection is associated with longer survival, but the role of surgery in this population subgroup is still debated⁹⁻₂⁵.

Radiotherapy is an essential part of treatment, and both standard and abbreviated courses have been employed with a median survival of 4-8 months²⁶⁻⁴¹. More recently, chemotherapy with temozolomide, alone or in association with different schedules of radiotherapy, has been advocated as an effective treatment in elderly patients with GBM⁴²⁻⁵⁰, although the potential neurological and hematological toxicity of the combination remains of concern.
We provide a review of the literature on the treatment of GBM in the elderly, with special attention to the role of chemotherapy in this population subgroup.

Overview of treatments

Surgery

Surgical resection is a critical aspect of the management of patients with GBM. The goals of resection include diagnosis, relief of mass effect, and cytoreduction. Systematic reviews have repeatedly found no convincing evidence for a survival advantage of surgery\(^{22-25}\), although some prospective and retrospective reports have found that gross total resection is associated with longer survival\(^{18-21}\). A large multicentric study of 788 patients with malignant gliomas accrued in North America between 1997 and 2001 found that resection was an independent favorable prognostic factor compared with biopsy only \((P < 0.0001)\), and the prognostic value was maintained in older patients\(^{10}\). A recent analysis of the impact of the extent of resection in a randomized trial of 243 patients with GBM showed longer survival in patients without residual tumor \(16.7 \text{ vs } 11.8 \text{ months, } P < 0.0001\). Survival benefit remained when patients were stratified for age \((>60 \text{ or } \leq 60 \text{ year})\), providing level 2b evidence that survival is associated with complete macroscopic resection\(^{19}\).

Few studies have reported on the effect of surgery in elderly patients with GBM. In a small series of 30 patients \(>65\) years of age with malignant glioma, who were randomized to receive stereotactic biopsy or resection of the tumor, the median survival was 171 days in the surgically treated group and 85 days in biopsied patients \((P = 0.035)\). Although there was a survival benefit of open surgery, the time of deterioration did not differ between the two treatment groups. Kelly and Hunt\(^{21}\) found only a modest prolongation of survival in 40 patients \(>65\) years old who underwent resection compared with 88 patients who underwent stereotactic biopsy \(27\) weeks \(\text{vs}\) \(15.4\) weeks). Surgery may also have a role as a palliative treatment to relieve neurological symptoms caused by tumor growth. Some functional improvement and better quality of life after surgery have been reported by several authors\(^{10,11,13}\).

In summary, the role of surgery remains unclear. Although some retrospective and prospective studies suggest that surgery prolongs survival, the poor quality of data mainly because of selection bias (i.e., good neurological status and tumors away from eloquent areas), does not allow for any definitive conclusion. Even if there is no such bias and all the effect is due to surgical resection, the reported maximum survival advantage is less than 6 months and less than 3 months in elderly patients.

Radiotherapy

Radiotherapy versus supportive care. Radiotherapy is frequently employed in elderly patients with GBM\(^{26-37}\) (Table 1). A recent multi-institutional randomized trial including 85 elderly patients \(\geq 70\) years of age compared radiotherapy \((50.4\ \text{Gy in 28 fractions})\) and supportive care with supportive care alone\(^{27}\). The median survival was 29.1 weeks with radiotherapy plus supportive care and 16.9 weeks with supportive care alone, with a median survival benefit of 12.2 weeks. Progression-free survival was 14.9 weeks in patients receiving radiotherapy and 5.4 weeks in patients receiving supportive care alone. It is noteworthy that radiotherapy did not cause further deterioration in the Karnofsky performance status (KPS), health-related quality of life or cognitive functions. Marijnen \textit{et al.}\(^{36}\) reported on 202 patients with GBM treated between 1990 and 2000. Irradiated patients survived significantly longer than non-irradiated patients \(10.6\ \text{vs}\ 1.9\) months), and survival benefit was maintained in patients \(>70\) years of age. Similar findings have been reported in several other series using both standard and shorter courses of radiotherapy\(^{26-30,36,39}\), suggesting that survival advantages of irradiation can be extended to elderly people with GBM.

Standard treatment versus hypofractionated radiotherapy. Only a few studies have reported on the use of standard radiotherapy in elderly patients with GBM. Mohan \textit{et al.}\(^{35}\) reported a median survival of 7.3, 4.5 and 1.2 months after standard radiotherapy, palliative radiotherapy and supportive care only, respectively, in 102 patients with GBM \(\geq 70\) years old and treated between 1976 and 1997. Villà \textit{et al.}\(^{30}\) reported a median survival of 45 weeks for elderly patients who received standard radiotherapy – 34 weeks for patients \(\geq 70\) and 55 weeks for patients between 65 and 70 years of age. Brandes \textit{et al.}\(^{35}\) reported a median survival of 11.2 months in 24 patients \(>65\) years of age treated with standard radiotherapy, with a 6- and 12-month survival of 83% and 31% respectively. In all reported studies, patients with a high KPS of at least 70 and good neurological status had a significantly better survival.

Data from several randomized and nonrandomized studies have suggested survival benefits in patients receiving shorter courses of radiotherapy (Table 1). Roa \textit{et al.}\(^{35}\) conducted a randomized prospective study on 100 patients with GBM of 60 years or older, treated with either standard radiotherapy or an abbreviated course of radiotherapy \((40\ \text{Gy in 15 fractions over 3 weeks})\). The median survival and 6-month survival were similar, 5.1 months and 44.7% in the standard radiotherapy group, and 5.6 months and 41.7% for abbreviated radiotherapy group \((P = 0.57)\). A randomized study of 474 adult patients with grade 3 or 4 astrocytoma compared two different radiation schedules of 60 Gy in 30 fractions and 45 Gy in 20 fractions. Analysis of a subgroup of 45 pa-
erly patients receiving standard radiotherapy. Com-

porated studies, the KPS was the strongest prog-

Table 1 - Main published series on radiotherapy and chemotherapy for elderly patients with glioblastoma

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients</th>
<th>Age (yr)</th>
<th>Fractionation dose (Gy)/fractions</th>
<th>CHT</th>
<th>Median PFS (mo)</th>
<th>Median survival (mo)</th>
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<td></td>
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<tr>
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<tr>
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<td>≥60</td>
<td>36/12</td>
<td>no</td>
<td>NA</td>
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<td>no</td>
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<td></td>
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<tr>
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<td>≥70</td>
<td>60/30</td>
<td>No</td>
<td>NA</td>
<td>4.1 (12% at 12 mo)</td>
<td></td>
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<td>NA</td>
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<td>NA</td>
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<td>45/25</td>
<td>PCV/BCNU</td>
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<td>60/30</td>
<td>PCV</td>
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<td>12.7 (56% at 12 mo)</td>
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<tr>
<td></td>
<td></td>
<td>≥65</td>
<td>60/30</td>
<td>TMZ2</td>
<td>10.7</td>
<td>14.9 (72.5% at 12 mo)</td>
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<td>≥70</td>
<td>60/30</td>
<td>TMZ2</td>
<td>6.7</td>
<td>10.8 (37% at 12 mo)</td>
<td></td>
</tr>
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<td>Combs Se et al., 2008</td>
<td>≥65</td>
<td>60/30</td>
<td>TMZ2</td>
<td>4</td>
<td>11 (48% at 12 mo)</td>
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<td>60/30</td>
<td>TMZ2</td>
<td>6</td>
<td>9.3 (35% at 12 mo)</td>
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<tr>
<td>Minniti G et al., 2008</td>
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<td>TMZ2</td>
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<td>13.7 (31% at 2 yr)</td>
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<td>60/30</td>
<td>TMZ4</td>
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PFS, progression-free survival; CHT, chemotherapy; BCNU, carmustine; PCV, procarbazine, vincristine, lomustine; TMZ, temozolomide.

1 Series included anaplastic astrocytomas and glioblastomas. 2 Five patients were treated with whole brain radiotherapy. 3 Adjuvant temozolomide. 4 Concomitant and adjuvant temozolomide. 5 Concomitant temozolomide.

Patients ≥60 years of age showed no difference in survival. Similar survival has been reported using doses of 30-50 Gy in 6-20 fractions. Bauman et al.26 reported a median survival of 6 months in a prospective study of 29 patients ≥70 years old with GBM, delivering a dose of 30 Gy in 10 fractions over 2 weeks. McAleeese et al.34 showed a 6-month survival of about 41% in 29 patients ≥70 years old using a regimen of 30 Gy in six fractions over 2 weeks, and a similar survival of 6 months has been reported by others using similar schedules37,38. In all reported studies, the KPS was the strongest prognostic factor for survival.

Toxicity of radiation treatment is of concern especially in the elderly. Acute toxicity requiring the interruption of treatment has been reported in up to 30% of elderly patients receiving standard radiotherapy30,35 compared with less than 10% of patients receiving short radiotherapy courses26,27,34,35. Although older patients may be more susceptible to neurobehavioral sequelae of cranial irradiation, only a few studies have shown significant radiation-induced late effects in older patients with GBM35,32. With respect to the health-related quality of life, few reports have shown no significant differences in the KPS scores over time after either standard or abbreviated courses of radiotherapy35,37. Similarly, radiotherapy plus supportive care does not have a detrimen-
tal effect on cognitive function compared with supportive care alone37. Risk of deficits after cranial radiotherapy in elderly patients is associated with high radiotherapy dose, larger field size, and the presence of co-morbidity. Using modern techniques like conformal radiotherapy or intensity-modulated radiotherapy, advanced planning imaging and software, the risks of neurocognitive deficits may be significantly reduced and are greatly overshadowed by deficits caused by the tumor itself.

In summary, radiotherapy is associated with increased survival of elderly patients with GBM without a significant detriment of cognitive function and health-related quality of life. Standard treatment can be considered for elderly patients with a good performance status, and age alone should not be the only reason for palliative treatment. In patients with poor prognostic factors (low KPS and neurological deficits), a short course radiotherapy may be preferable because it shortens the treatment time, offering survival benefits similar to those obtained with conventional radiotherapy. Fr-
Some studies have reported that MGMT promoter among patients with GBM treated with temozolomide and standard radiotherapy, whereas patients with unmethylated MGMT promoters did not have such survival benefit from combination chemotherapy. The 2-year survival rates for unmethylated and methylated MGMT promoters treated with standard radiotherapy and temozolomide were 14% and 46%, respectively.

Temozolomide has been recently employed alone and in association with radiotherapy as an initial treatment for elderly patients with GBM (Table 1). Chinot et al. reported on 22 patients >70 years of age with GBM who received exclusive treatment with temozolomide. The reported median survival was 6.4 months and progression-free survival was 5.0 months. The 6-month and 12-month survival rates were 60% and 25%, respectively. Half of the patients were able to decrease their steroid dosage or to improve their performance status during the treatment. Grade 3 or 4 hematologic toxicity occurred in 15% of patients, necessitating dose delay or reduction in 13% and 14% of patients, respectively. Glantz et al. reported a median survival of 6 months (11.9% at 1 year) in 30 patients ≥70 years old who were treated with temozolomide (150–200 mg/m² for 5 days every 4 weeks) as first-line treatment. The only toxicity noted was occasional myelosuppression, which required delay or reduction of the scheduled dose in 15% of patients. Similar results have been reported by others, suggesting that temozolomide is a safe and effective treatment and may be considered for the treatment of elderly patients with GBM.

### Concurrent temozolomide and radiotherapy

The recent published randomized European and Canadian trial (European Organisation for Research and Treatment of Cancer; EORTC 26981/22981-NCIC) has clearly demonstrated that the addition of temozolomide to radiotherapy, followed by 6 monthly cycles of temozolomide, provides significant survival benefit with minimal additional toxicity in patients with GBM. The reported median survival was 14.6 months with radiotherapy plus temozolomide and 12.1 months with radiotherapy alone, with respective 2-year survival rates of 27% and 10%, respectively. Currently, the standard treatment for adult patients with GBM consists of surgery followed by radiotherapy plus concomitant and adjuvant temozolomide.

Few studies have reported on the use of standard radiotherapy and temozolomide in elderly patients. Using this regimen, we found a median survival of 10.8 months and a median progression-free survival of 6.7 months in 32 elderly patients ≥70 years of age presenting with good prognostic factors (macroscopic resection, high KPS and good neurological status). The 6- and 12-month survival rates were 91% and 36%, respectively, with respective 6- and 12-month progression-free survival rates of 56% and 16%. A partial response was observed in 22% of patients and a minimal

**Treatments of Glioblastoma in Elderly Patients**

Nitrosourea-based chemotherapy. The role of chemotherapy as an alternative treatment in elderly patients with GBM has been poorly investigated, mainly because of concern about chemoresistance and the potential severity of side effects in such patients. An improved survival in elderly patients with GBM treated with nitrosourea-based chemotherapy and radiotherapy has been reported in a few studies. In a retrospective study of 148 patients who received nitrosourea-based chemotherapy, median survival was 43 weeks in patients ≤60 but only 24 weeks in patients >60 years of age (P <0.001). Serious myelosuppressive complications occurred in 35% of patients >60 years and in 16% of patients ≤60 years old. Pierga et al. reported that survival was longer in 12 patients >70 years old who were treated with nitrosourea-based chemotherapy than in patients treated with radiotherapy alone (58 vs 27 weeks), but 4 of the 12 patients who received chemotherapy experienced WHO grade 3-4 hematological toxicity. Brandes et al. reported a survival of 12.7 months in 32 elderly patients treated with standard radiotherapy and procarbazine-lomustine-vincristine chemotherapy. The 6- and 12-month survival was 90.6% and 56.2%, respectively. Grade 3-4 toxicity.

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response in 18% of patients. Hematologic toxic effects occurred in 6% of patients during concomitant RT and temozolomide, and in 22% of patients during adjuvant temozolomide chemotherapy.

Brandes et al. \( ^{20} \) analyzed the outcome in 58 patients ≥ 65 years old with GBM treated with standard radiotherapy and temozolomide. Sixteen patients (43%) presented MGMT promoter methylated and 21 unmethylated (57%) status. The median progression-free survival was 22.9 months in patients with MGMT promoter methylated status and 9.5 months in patients with unmethylated MGMT promoter status. The 2-year overall survival was 31%-83% in patients with methylated MGMT promoter status, suggesting that the prognostic and predictive value of MGMT methylation is also maintained in the elderly population. Five patients (8%) interrupted concomitant or adjuvant chemotherapy for grade 4 hematological toxicity; in 2 of them levels returned to normal and temozolomide was continued as maintenance treatment.

Combs et al. \( ^{47} \) reported on 43 patients ≥ 65 years old with GBM treated with postoperative standard radiotherapy and concomitant temozolomide. Median survival was 11 months, with 1-year and 2-years survival rates of 48% and 8%, respectively. Median progression-free survival was 4 months – 41% at 6 months and 18% at 12 months. Four patients developed Grade 3 or 4 hematological side effects, which led to early discontinuation of temozolomide in one patient. In all reported studies, KPS and neurological status were the most important factors predictive of survival.

Aggressive treatment may be associated with high neurological toxicity in elderly patients. In 58 patients treated with standard radiotherapy and temozolomide, grade 2 and grade 3 mental status deterioration were detected in 31% and 25% of patients, respectively.\(^ {50} \) Minniti et al. \( ^{45} \) reported that 40% of patients experienced neurological deterioration during or immediately after standard radiotherapy, including grade 2/3 confusion and/or somnolence, memory loss, and expressive dysphasia. Magnetic resonance imaging showed an increase in peritumoral edema or diffuse leukoencephalopathy without evidence of tumor progression. Similarly, in a small series of 19 elderly patients treated with radiotherapy and temozolomide, 42% of patients treated with chemoradiotherapy experienced grade 3 or 4 toxicity versus none in patients treated with radiotherapy alone.\(^ {46} \) Although the neurocognitive decline occurring after concomitant and adjuvant treatment in GBM patients is multifactorial and may be due to the disease itself, surgery and age-related comorbidity, future studies need to further investigate the high potential incidence of cognitive deficit in elderly GBM patients treated with standard radiochemotherapy.

We recently reported on 43 elderly patients ≥ 70 years of age treated with abbreviated radiotherapy (6 fractions of 5 Gy for a total of 30 Gy over 2 weeks) followed by up to 12 cycles of adjuvant temozolomide (150-200 mg/m\(^2\) for 5 days during each 28-day cycle)\(^ {49} \). The median survival and progression-free survival rates were 9.3 months and 6 months, respectively (\(P < 0.01\)). The 6- and 12-month overall survival rates were 86% and 35%, respectively, and respective progression-free survival were 55% and 12%. Grade 2-3 neurological deterioration occurred in less than 20% of patients and was reversible with the use of steroids in half the patients. Severe myelosuppression occurred in approximately one third of the patients, leading to early discontinuation of chemotherapy in 15% of patients. An ongoing EORTC/RTOG (Radiation Therapy Oncology Group) randomized trial is comparing short-term radiotherapy (40 Gy in 15 fractions over 3 weeks) to concomitant short-term radiotherapy plus concomitant and adjuvant temozolomide in elderly patients > 65 years old with GBM.

In summary, temozolomide shows survival benefits in elderly patients with GBM and may be an appropriate treatment in such a population. The combination of radiotherapy and temozolomide is associated with a longer survival but should be considered only in selected elderly patients who present with good prognostic factors because of the risk of significant toxicity. Alternatively, a short course of radiotherapy and adjuvant temozolomide may represent a reasonable therapeutic approach in patients because it prolongs survival and maintains an acceptable quality of life. The impact of different schedules of radiotherapy plus temozolomide on survival and quality of life and the role of MGMT expression in the treatment of elderly patients with GBM need to be addressed in future randomized studies.

**Present and future perspectives**

GBM is characterized by several aberrantly activated signaling pathways. Several growth factor receptors, such as EGFR, VEGFR, and PDGFR, are overexpressed, amplified, and/or mutated, leading to uncontrolled cell proliferation, angiogenesis, migration, survival and differentiation.\(^ {57},^{58} \) Several phase I/II clinical trials have evaluated the use of growth factor receptor inhibitors, antiangiogenic therapies, and integrin inhibitors in patients with GBM.

Gefitinib and erlotinib, two main EGFR small molecule tyrosine kinases inhibitors, have been evaluated as single agents in patients with recurrent GBM, but with minimal or no effect on survival.\(^ {59-61} \) However, in a subset of patients with co-expression of normal PTEN and mutant EGFRvIII and combined low levels of AKT and overexpression of EGFR, survival benefits have been suggested in some recent studies.\(^ {62-64} \) More recently, studies testing the combination of erlotinib in association with radiotherapy and/or temozolomide have reported conflicting results.\(^ {65},^{66} \) Using
this regimen, Prados et al. showed a median progression-free survival of 8.2 months and median survival of 19.3 months. In contrast, a recent study of the North Central Cancer Treatment Group using a similar regimen showed no significant additional benefit for erlotinib when combined to radiotherapy and temozolomide. Moreover, the regimen was associated with significant toxicity, including two cases with grade 5 toxicity (non-neutropenic pneumonia). So far, the potential role of erlotinib in association with temozolomide and radiotherapy remains unclear.

Bevacizumab (Avastin, Genentech, San Francisco, CA, USA), a humanized monoclonal antibody that selectively blocks the vascular endothelial growth factor (VEGF), has shown survival benefits in patients with recurrent malignant glioma. A phase II trial of bevacizumab and irinotecan in recurrent GBM showed a 6-month progression-free survival and overall survival of 46% and 77%, respectively, and similar results have been reported by others. Based on the clinical evidence, the US Food and Drug Administration Oncologic Drugs Advisory Committee recently approved the use of bevacizumab as a single agent for patients with progressive GBM following prior therapy. The association of radiotherapy, temozolomide and bevacizumab is promising, and an RTOG multicenter phase III study of bevacizumab in combination with chemoradiation is in the planning stage.

Integrins are cell adhesion molecules that play a role in cell adhesion, cell migration, and proliferation during angiogenesis. Cilengitide (Merck KgaA, Darmstadt, Germany) inhibits α5β3 and αvβ5 integrins, which are specifically involved in angiogenesis, and has shown modest antitumor activity among recurrent GBM patients. Preliminary results of a phase II trial of cilengitide added to radiotherapy and temozolomide conducted on 52 patients with newly diagnosed GBM have suggested efficacy in a subgroup of patients with methylated MGMT promoter, with no added toxicity. An EORTC multicenter phase III trial is currently evaluating the association of radiotherapy, temozolomide, and cilengitide.

Several other new targeted agents have been identified to potentially treat these tumors. Multiple growth factor inhibitors of VEGFR/PDGF vatalanib (PTK787/ZK222584 Novartis), sunitinib (Sutent, Pfizer), sorafenib ( Nexavar, Bayer), and cediranib (Rocitin, AstraZeneca) are currently being investigated in phase I/II studies. Other potential targeted therapy includes the inhibitor of EGFR/VEGFR-2 Vandetanib (Zactima, AstraZeneca), the multiple growth factor inhibitor imatinib mesylate (Gleevec, Novartis), farnesyl transferase inhibitors lonafarnib (sarasar, Shering-Plough) and tipifarnib (Zarnestra, Johnson & Johnson), and mTOR inhibitor temsirolimus (Torisel, Wyeth Pharmaceuticals).

Since most of these targeted drugs have been employed in elderly patients affected by other cancers with acceptable toxicity, it is likely that combination of cytostatic and cytotoxic drugs will also play a role in the treatment of elderly patients with GBM, provided that they are effective in large randomized clinical trials. Future therapeutic strategies should therefore include: 1) a combination of targeting with alkylating agents and/or radiotherapy to overcome therapeutic resistance in randomized clinical trials; 2) a combination of different molecular-targeted agents able to inhibit different signal transduction pathways, and 3) determination of the genetic changes and molecular pathways involved in GBM, which will potentially allow the design of individualized therapies for subgroups of patients based on molecular characteristics of the tumor.

Conclusions

Current treatment of GBM in the elderly includes surgery, radiotherapy and chemotherapy. However, due to lack of large randomized studies in such a population, the optimal management of GBM in the elderly is still debated. Randomized and prospective studies indicate that both standard and short courses of radiotherapy are associated with longer survival than obtained with supportive care only. Chemotherapy with temozolomide is a safe and feasible treatment that has shown survival benefits in this subgroup of patients. Promising survival has been reported with the addition of concomitant and/or adjuvant temozolomide to standard radiotherapy in elderly patients with GBM with good prognostic factors, but the toxicity of aggressive treatments remains a concern. The impact of different schedules of radiotherapy plus temozolomide on survival and quality of life in the treatment of elderly patients with GBM needs to be addressed in future randomized studies.

Molecular characterization of GBM is contributing to the identification of patients who could theoretically benefit from new targeted drugs. In this scenario, the major challenge is to select the targeted agents which can translate to a survival benefit in patients with GBM. Bevacizumab is the first targeted agent approved in the USA for the treatment of recurrent GBM. Clinical evaluation of several other growth factor receptor inhibitors, antiangiogenic agents, and integrin inhibitors in combination with alkylating drugs and radiotherapy is currently ongoing and represents a promising strategy in patients with GBM that could be extended to the elderly population.

References

3. Jukich PJ, McCarthy BJ, Surawicz TS, Freels S, Davis FG:


