Adjuvant treatment of high grade gliomas

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introduction

Gliomas are the most frequent primary brain tumours in adults. They are usually classified and graded according to the World Health Organisation (WHO) criteria [1]. Most gliomas are considered diffuse glioma, which refers to their infiltrative growth pattern. Histologically, they are classified into astrocytoma, oligodendroglioma, oligoastrocytoma (which at the genetic level are either oligodendroglioma or astrocytoma) and ependymoma (which are rather rare). Low-grade tumours have a median survival of 5–15 years, but median survival is between 2 and 4 years for anaplastic astrocytoma and only 12–15 months for the most malignant primary brain tumour, the glioblastoma multiforme (GBM).

No matter how extensive a glioma is resected, due to the infiltrative nature of the tumour, resection will never be ‘radical’ from the surgical point of view. Moreover, it has been shown that the surgeon’s estimate of the extent of resection made during surgery is unreliable, and magnetic resonance (MR) spectroscopy or positron emission tomography (PET) imaging may reveal tumour in areas that are considered normal on standard T1 and T2 weighted MR imaging [2–4]. In addition, due to the localization of the tumour in eloquent areas often only a limited resection or just a biopsy is possible. Thus, in contrast to other diseases in oncology where adjuvant treatment is given to eradicate microscopic disease, in glioma, post-surgical adjuvant treatment is indicated to treat macroscopic disease. The goal of the adjuvant treatment is not to cure the patient, as in virtually all patients the tumour will eventually recur, but to prolong overall survival in a clinically good condition.

Several recent trials both in high-grade and in low-grade tumours have shown increased progression-free survival without affecting overall survival after more intense treatment at first diagnosis [e.g. early radiotherapy, adjuvant procarbazine-lomustine-vincristine (PCV) chemotherapy] [5–7]. Postponing progression may help to keep the neurological condition of a brain tumour patient stable, but whether indeed in general quality of life is improved by aggressive initial treatment in newly diagnosed patients is unknown. Salvage chemotherapy at the time of progression allows the determination of responsiveness of the tumour, which is usually not possible in patients treated with adjuvant chemotherapy after radiotherapy. Thus, in the case of adjuvant chemotherapy, patients with chemotherapy-resistant tumours will receive the full series of chemotherapy without any benefit.

Randomised controlled clinical trials conducted from 1970 to the 1990s have demonstrated that radiotherapy (RT) to a dosage of 60–64 Gray (Gy) improves the survival of high-grade glioma patients (Table 1) [8–10]. Furthermore, radiotherapy with or without chemotherapy was found to be more effective than chemotherapy alone [8, 11, 12]. Attempts to increase survival further with RT-dose intensification have not been successful [13–15]. This implies that for further improvement of treatment outcome other treatment modalities are required [13–15].

chemotherapy

Virtually all trials on ‘classical’ adjuvant chemotherapy, administered sequentially with radiotherapy and usually with nitrosourea (carmustine, lomustine) failed to improve overall outcome [11, 16]. It took a large, individual patient database meta-analysis comprising over 3000 patients to show that this kind of adjuvant chemotherapy may indeed result in a very modest 5% increase in 2-year survival (from 15% to 20%; Table 1) [17]. In recent years the role of chemotherapy in glioma has been met with renewed interest mainly due to two developments: the improved outcome of GBM treated with concurrent radiotherapy and daily temozolomide (TMZ) followed by six cycles of adjuvant temozolomide; and the recognition of the sensitivity to chemotherapy of 1p/19q loss oligodendroglialomas.

temozolomide for patients with newly diagnosed glioblastoma multiforme

After the phase II trial by Stupp et al. demonstrated the safety of daily low-dose TMZ (75 mg/m² daily 7 day/week) combined with radiotherapy for up to 7 weeks, followed by six cycles of adjuvant TMZ (5 days q28 days) the European Organisation for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCI-C) Clinical Trials Group compared this combined chemoradiation regimen to standard radiotherapy alone in a large prospective randomised phase III trial in 573 patients [18, 19]. This study unequivocally demonstrated that the combination of TMZ and radiotherapy followed by up to six cycles of adjuvant TMZ improves survival. Patients randomised to the combined modality treatment received daily 75 mg/m² for the entire 6-week period of radiotherapy (also at the weekends), and after the end of radiotherapy six cycles of adjuvant treatment given at 150–200 mg/m² on day 1–5 every 4 weeks (Figure 1). Patients received Pneumocystis carinii pneumonia prophylaxis during the concomitant phase with oral cotrimoxazol or pentidine.
inhalations, and during the adjuvant phase anti-emetic treatment with 5-hydroxytryptamine-3 (5HT3) antagonists. With this combined modality treatment the 2-year survival increased from 10% to 27% (Table 1). Patients with a modest performance status showed limited if any benefit from the addition of chemotherapy; for patients having undergone a biopsy only, the benefit was statistically not significant (which may have been due to the limited number of patients in this group). Overall, the combined treatment was well tolerated; the main reason for early discontinuation was disease progression. Quality of life analysis using the EORTC C30 and the brain cancer specific module BCM20 showed that the combined modality treatment did not have significant adverse effects on the quality of life [20].

Table 1. Median, 1- and 2-year survival after various postoperative adjuvant treatment in high grade glioma

<table>
<thead>
<tr>
<th>Reference</th>
<th>Treatment</th>
<th>Median survival (months)</th>
<th>1-year survival</th>
<th>2-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walker [8]</td>
<td>Supportive care</td>
<td>3</td>
<td>3%</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>BCNU</td>
<td>4</td>
<td>12%</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>RT</td>
<td>8</td>
<td>24%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>RT + BCNU</td>
<td>8</td>
<td>32%</td>
<td>5%</td>
</tr>
<tr>
<td>Glioma Meta-analysis Trialists [17]</td>
<td>RT</td>
<td>40%</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>EORTC 26981 [19]</td>
<td>RT</td>
<td>12</td>
<td>51%</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>RT + temozolomide</td>
<td>15</td>
<td>61%</td>
<td>27%</td>
</tr>
</tbody>
</table>

The outcome of EORTC study 26981 is given in bold. RT, radiotherapy; CTX, chemotherapy; SRS, stereotactic radiosurgery; BCNU, carmustine.

The clinical relevance of the mechanistic implication of the DNA repair enzyme alkyltransferase in alkylating chemotherapy was tested in the randomised EORTC/NCIC trial on GBM. Samples from 206 patients could be analysed for the status of the MGMT gene promoter using methylation-specific polymerase chain reaction (PCR) [25]. In 45% of the tumour samples the MGMT gene promoter was methylated and thus the gene was silenced. Overall, patients with a silenced MGMT gene had a longer survival. Breakdown of the data by treatment strongly suggests that the MGMT methylation status is a predictive marker for benefit from TMZ chemotherapy. For patients in the TMZ/RT arm the 2-year survival rate was 46% when their tumour presented a methylated MGMT status in contrast to only 14% in patients with an unmethylated MGMT gene promoter (Table 2). Thus, in this molecularly defined subgroup TMZ appears even more effective increasing the median survival by 9 months to 21.7, while patients with an unmethylated MGMT gene promoter had little if any TMZ-derived benefit with a median survival of 12.7 months. A confirmation of these findings and validation of assays is required before this test can be used in daily clinical practice.

Table 2. Median survival and 2-year survival in EORTC study 26981 in relation to the methylation status of the MGMT promotor [25]

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median survival (months)</th>
<th>2-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Radiotherapy</td>
<td>Radiotherapy plus temozolomide</td>
</tr>
<tr>
<td>Unmethylated MGMT promotor</td>
<td>11.8 months</td>
<td>12.7 months</td>
</tr>
<tr>
<td>Methylated MGMT promotor</td>
<td>15.3 months</td>
<td>21.7 months</td>
</tr>
</tbody>
</table>

*72% of the patients in the radiotherapy-arm received alkylating chemotherapy at recurrence.

O6-methylguanine DNA methyltransferase

Both nitrosoureas and TMZ act as DNA alkylating and methylating agents. Alkylation of the O6-position of guanine is one among many DNA adducts formed, but it is of major importance for the induction of mutations and for the cytotoxic action of these drugs. During subsequent DNA replication, the methylated guanine pairs with thymidine instead of cytidine, which incites futile mismatch repair and eventually may induce apoptosis. Cells have the capacity of restoring guanine through the DNA excision repair enzyme O6-methylguanine-DNA methyltransferase (MGMT), also known as O6-alkyl-guanine-alkyltransferase (AGAT), during which process the enzyme is inactivated (see review by Gerson et al.) [21]. High endogenous MGMT activity in cancer cells blunts the treatment effect of alkylating agent chemotherapies creating a resistant phenotype, whereas the absence of MGMT or the inability to produce MGMT makes the cell vulnerable to alkylating agents. Indeed, silencing of the MGMT gene by promoter methylation that impairs expression of the DNA repair enzyme has been associated with prolonged survival in glioma patients treated with nitrosourea’s or with TMZ [22–24].

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**treatment of elderly and of poor prognosis GBM patients**

Several investigators have tried to shorten the treatment period for poor prognosis patients (usually defined as patients in poor clinical condition, or with an age over 65–70 years) by giving...
hypofractionated radiotherapy. A Canadian randomized trial in elderly patients recently showed that indeed there is no survival differences between standard 60 Gy RT and a shortened course of RT (40 Gy in 15 fractions) in patients over 70 years of age [26]. The advantage of this shortened schedule in elderly patients is of course the much shorter treatment duration. Many institutions have a conservative approach to elderly patients and often only offer best palliative care without radiotherapy. A French study in anaplastic glioma patients over 70 years of age with a Karnofski performance status (KPS) of 70 or higher compared 50 Gy in 28 fractions to best palliative care [27]. Radiotherapy increased progression-free survival from 7 to 14 weeks and median survival from 18 to 29 weeks. Thus, although radiotherapy clearly increases survival, the increase in survival after radiotherapy is modest and even after radiotherapy the outlook is poor. One may consider treating elderly patients only if they are in a good condition, in which case a short course of radiotherapy may be appropriate. Once it became clear that adding daily TMZ to radiotherapy improved outcome in GBM patients (even in the age cohort 60–70 years), the obvious question was whether patients over 70 years of age and patients treated with a short radiotherapy schedule also benefit from the addition of TMZ. One may assume that if a benefit is present this will be less significant, but this needs further study.

Because of reports of high response and disease stabilisation rates with TMZ chemotherapy in previously untreated GBM patients [28], chemotherapy instead of radiotherapy has been evaluated in a limited number of elderly patients in controlled trials. One prospective study on 32 patients reported a median survival of 6.4 months [29]. A second (non-randomized) trial observed a survival outcome after treatment with TMZ (n = 32) that was at least as good as ‘historical controls’ with similar prognostic characteristics treated with radiotherapy in the same time period within the same institution [30]. The treatment outcome of these two studies appears similar compared with the results of radiotherapy only in elderly or poor prognosis GBM patients [26, 31]. In both studies toxicity was modest, although in one study dose delays and dose reductions were needed in 38% and 13% of patients. This underlines the need for a more cautious approach to chemotherapy in elderly patients.

Several new randomized studies are exploring the role of concomitant TMZ with radiotherapy (either short course or the full 60 Gy schedule) or treatment with TMZ only. Of course, one goal here is to avoid too intensive treatments of long duration in a frail population with a limited prognosis.

**adjuvant chemotherapy in anaplastic oligodendroglioma and oligoastrocytoma**

Oligodendroglioma and, to a lesser extent, oligoastrocytoma are responsive to chemotherapy. Two-thirds of patients with recurrent tumours were shown to respond to PCV chemotherapy or to TMZ [32–34]. Further molecular studies showed that in particular patients with oligodendrogliomas with loss of heterozygosity on both the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) are very sensitive to PCV and to TMZ chemotherapy, although the underlying mechanism is still unclear [34–36]. The recent finding of a high percentage of these tumours with a methylated MGMT status (>80%) may at least in part explain this sensitivity [37].

Both the RTOG and the EORTC investigated the addition of PCV chemotherapy to radiotherapy in newly diagnosed anaplastic oligodendroglioma [6, 7]. The RTOG study used a neo-adjuvant dose-intensified PCV schedule, whereas the EORTC study used a classical adjuvant design with standard PCV. In both studies the control arm received radiotherapy only, but further treatment at the time of progression was left to the discretion of the treating physician. Most patients received further chemotherapy at the time of progression. Although both studies observed an increase in progression-free survival in the PCV arm, this did not translate in an increase in overall survival (Table 3). In contrast to the EORTC study, the RTOG study did not observe an increase in progression-free survival in the non-1p/19q deleted tumours. Patients with 1p/19q loss had a clearly better outcome (median survival over 6–7 years compared with 2–3 years in patients without 1p/19q loss), but this improved outcome was regardless of treatment (data not shown). Both studies show, that in this relatively chemosensitive tumour the timing of chemotherapy is not relevant (at first diagnosis or at recurrence), as long as it is given.

Despite the absence of a formal trial many clinicians today propose upfront TMZ as first treatment in 1p/19q loss oligodendroglioma. This is an unproven approach, in part based on the assumption that RT is likely to induce delayed cognitive deficits. This assumption is questionable if modern RT techniques are used with dose fractions of less than 2 Gy [38]. Eventually, this may be more a matter of side-effects and one should realize that especially for limited size lesions RT offers an effective treatment of short duration (6 weeks instead of 12–24 months of chemotherapy) with prolonged tumour control.

**anaplastic astrocytoma**

Past trials in general showed similar outcome to ‘classical’ adjuvant chemotherapy of anaplastic astrocytoma compared with GBM [16]. With the improved outcome after treatment with adjuvant and concomitant TMZ in GBM (see the section on GBM), the question is whether this treatment should also be given to anaplastic astrocytoma [19]. In view of the superior outcome of combined modality treatment this seems logical, but it is at present unknown if combined modality treatment may cause an increased delayed neurotoxicity in patients with a longer survival. Whatever the explanation, the currently

### Table 3. Median overall survival and progression-free survival in EORTC study 26951 and RTOG study 94-02 with adjuvant PCV in anaplastic oligodendroglioma

<table>
<thead>
<tr>
<th></th>
<th>Overall survival</th>
<th>Progression-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RT</td>
<td>RT/PCV</td>
</tr>
<tr>
<td>EORTC 26951 [7]</td>
<td>30.6 months</td>
<td>40.3 months</td>
</tr>
<tr>
<td>RTOG 94-02 [6]</td>
<td>4.7 years</td>
<td>4.9 years</td>
</tr>
</tbody>
</table>

RT, radiotherapy; RT/PCV, radiotherapy followed by adjuvant PCV chemotherapy.
available data fail to provide any evidence that the increased chemosensitivity of recurrent anaplastic astrocytoma compared with GBM is reflected in a higher response rate to neoadjuvant chemotherapy [39]. Reviews of old RTOG/ECOG studies suggested a decreased survival in more aggressively treated anaplastic astrocytoma patients [40]. These data were, however, obtained from historical comparisons over trials, so the conclusions should be viewed with caution. It probably cannot be taken for granted that approaches showing a superior outcome in GBM will also provide a superior outcome in anaplastic astrocytoma.

conclusions

Concurrent chemo-irradiation with TMZ is now considered standard of care for adult GBM patients. It is yet unclear if these results can also be extrapolated to other anaplastic glioma. Adjuvant or neoadjuvant PCV chemotherapy does not improve overall survival in anaplastic oligodendroglioma/oligoastrocytoma, regardless of genotype, but may prolong progression-free survival.

references