Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial

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Summary

Background Radiotherapy is the standard care in elderly patients with malignant astrocytoma and the role of primary chemotherapy is poorly defined. We did a randomised trial to compare the efficacy and safety of dose-dense temozolomide alone versus radiotherapy alone in elderly patients with anaplastic astrocytoma or glioblastoma.

Methods Between May 15, 2005, and Nov 2, 2009, we enrolled patients with confirmed anaplastic astrocytoma or glioblastoma, age older than 65 years, and a Karnofsky performance score equal to or higher than 60. Patients were randomly assigned 100 mg/m² temozolomide, given on days 1–7 of 1 week on, 1 week off cycles, or radiotherapy of 60·0 Gy, administered over 6–7 weeks in 30 fractions of 1·8–2·0 Gy. The primary endpoint was overall survival. We assessed non-inferiority with a 25% margin, analysed for all patients who received at least one dose of assigned treatment. This trial is registered with ClinicalTrials.gov, number NCT01502241.

Findings Of 584 patients screened, we enrolled 412. 373 patients (195 randomly allocated to the temozolomide group and 178 to the radiotherapy group) received at least one dose of treatment and were included in efficacy analyses. Median overall survival was 8·6 months (95% CI 7·3–10·2) in the temozolomide group versus 9·6 months (8·2–10·8) in the radiotherapy group (hazard ratio [HR] 1·09, 95% CI 0·84–1·42, p=0·033). Median event-free survival (EFS) did not differ significantly between the temozolomide and radiotherapy groups (3·3 months [95% CI 3·2–4·1] vs 4·7 [4·2–5·2]; HR 1·15, 95% CI 0·92–1·43, p=0·043). Tumour MGMT promoter methylation was seen in 73 (35%) of 209 patients tested. MGMT promoter methylation was associated with longer overall survival than was unmethylated status (11·9 months [95% CI 9·0 to not reached] vs 8·2 months [7·0–10·0]; HR 0·62, 95% CI 0·42–0·91, p=0·014). EFS was longer in patients with MGMT promoter methylation who received temozolomide than in those who underwent radiotherapy (8·4 months [95%CI 5·5–11·7] vs 4·6 [4·2–5·0]), whereas the opposite was true for patients with no methylation of the MGMT promoter (3·3 months [3·0–3·5] vs 4·6 months [3·7–6·3]). The most frequent grade 3–4 intervention-related adverse events were neutropenia (16 patients in the temozolomide group vs two in the radiotherapy group), lymphocytopenia (46 vs one), thrombocytopenia (14 vs four), raised liver-enzyme concentrations (30 vs 16), infections (35 vs 23), and thromboembolic events (24 vs eight).

Interpretation Temozolomide alone is non-inferior to radiotherapy alone in the treatment of elderly patients with malignant astrocytoma. MGMT promoter methylation seems to be a useful biomarker for outcomes by treatment and could aid decision-making.

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Introduction

Gliomas account for half of all intrinsic brain tumours. WHO grade IV glioblastomas are the most malignant variant of glioma and make up around half of such tumours. At a population level, median survival for patients with glioblastoma remains less than 6 months, and age is the most important therapy-independent prognostic factor. In a few years, more than half of patients with glioblastoma will be elderly (older than 65 years). Anaplastic astrocytoma (WHO grade III), a less common malignant glioma with an overall better prognosis than grade IV glioblastoma, shares molecular features and poor outcome with glioblastomas in the elderly. The current standard of care in elderly patients with glioblastoma or anaplastic astrocytoma is resection or biopsy followed by involved-field radiotherapy. The classic radiotherapy treatment schedule is 60 Gy in 30 fractions of 2·0 Gy, although hypofractionated schedules, such as 15 fractions of 2·66 Gy, are used in some centres. Concomitant and adjuvant radiochemotherapy with the alkylating agent temozolomide has become the standard of care in non-elderly patients with glioblastoma. The benefit from this treatment, however, is largely restricted to patients with tumours exhibiting promoter methylation of the O⁶-methylguanine-DNA methyltransferase gene (MGMT), which encodes a DNA repair protein associated with alkylator resistance.

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Articles
Increasing age is associated with decreasing benefit from chemotherapy and an increasing risk of cognitive side-effects from cranial irradiation. Moreover, the tolerability of combined radiotherapy and temozolomide seems to be reduced in the elderly. Temozolomide chemotherapy alone has shown promising results in elderly patients with glioblastoma. We have previously reported encouraging progression-free survival at 6 months in patients with recurrent glioblastoma treated with a 1 week on, 1 week off regimen. On the basis of these results the German Neuro-oncology Working Group (NOA) has done a randomised, phase 3 trial (NOA-08) to assess whether dose-dense temozolomide alone is inferior to radiotherapy alone in the management of newly diagnosed glioblastoma or anaplastic astrocytoma in elderly patients, and to investigate the role of MGMT promoter methylation.

**Patients and methods**

**Patients**

Between May 15, 2005, and Nov 2, 2009, we recruited patients from 23 university centres across Germany and one in Switzerland. Eligible patients had de-novo anaplastic astrocytoma or glioblastoma that were histologically confirmed locally after biopsy or resection, age older than 65 years, and a Karnofsky performance score of 60 or more. Histological diagnoses were confirmed centrally at study entry by the Brain Tumour Reference Centre, German Society for Neuropathology and Neuroanatomy, Düsseldorf, Germany. For patients recruited up to the end of 2006, the 2000 WHO classification was used, and the 2007 classification was used thereafter. Patients who had undergone previous systemic chemotherapy or radiotherapy to the brain or who had inadequate bone-marrow reserve, liver function, or renal function were excluded. The trial was approved by the ethics committees of all participating sites and all patients provided written informed consent.

**Randomisation and masking**

Patients were assigned to treatment groups in a 1:1 ratio. Randomisation was done centrally by an independent contract research organisation, Alcedis, in Giessen, Germany. A randomisation list was generated electronically, in blocks of variable length without stratification, before the start of the study.

Enrolment was done at each study site by an investigator. Assignment was initiated by fax transmission from the study site to the contract research organisation for each patient who fulfilled the eligibility criteria. A project manager reported the next available number on the assignment list to the trial investigator via fax transmission to the study site.

The differences in study treatments made masking of assignment for investigators or patients impossible. We aimed to prevent bias by strict adherence to an analysis plan that was written by the statistician (CM) and approved by the lead investigators (WW and MW) before analysis of any data.

**Procedures**

Patients were assigned temozolomide alone or radiotherapy alone. Temozolomide was administered according to a 1 week on, 1 week off schedule, with 100 mg/m² given on days 1–7 (figure 1). Dose increases or decreases in 25 mg/m² steps were based on blood-cell counts and general tolerability. Radiotherapy was administered to the gross tumour volume plus a 2 cm margin over 6–7 weeks, in fractions of 1·8–2·0 Gy, to a total 60·0 Gy, according to preoperative MRI and dedicated CT or three-dimensional planning systems.

In the case of disease progression, patients in the temozolomide group received radiotherapy as appropriate and those in the radiotherapy group received temozolomide as appropriate, and surgery or other treatments were considered. If toxic effects of temozolomide resulted in delays of longer than 4 consecutive weeks before the completion of 6 months of therapy, treatment was stopped and the patient underwent radiotherapy. Treatment was stopped for...
disease progression or unacceptable toxic effects (grade 4 toxic effects and subjective patient-related factors), which were graded according to the common terminology criteria for adverse events, version 3.0. Adverse events were reported by investigators with free-text descriptions on an adverse-event form and classified into 12 main categories by WW.

Baseline assessments included physical examination, MRI, full blood-cell counts, blood chemistry, minimental state examination, and the European Organisation for Research and Treatment of Cancer (EORTC) QLQ C-30 and QLQ-BN-20 quality-of-life questionnaires. During treatment, patients underwent monthly clinical assessments. Additionally, 3 months after the start of temozolomide and every 3 months thereafter, or 4 weeks after the completion of radiotherapy, patients were assessed with MRI, mini-mental state examination, and the quality-of-life questionnaires.

In the temozolomide group, full blood-cell counts were done weekly and blood chemistry was done every 4 weeks during treatment. In the radiotherapy group, full blood-cell counts and blood chemistry were done every 4 weeks after the start of treatment. Toxic effects were assessed every 2 weeks.

Tumour response or progression were defined according to the Macdonald criteria: complete response, partial response, stable disease, or progressive disease on MRI. An apparent increase in tumour volume or contrast enhancement in the radiation field on the first scan after radiotherapy was started was not taken to be disease progression, but was assessed with MRI 4–6 weeks later. Patients with complete resection who had non-measurable disease—ie, only unidimensionally measurable lesions, masses without clearly defined margins, or lesions less than 10 mm in diameter—could not achieve a complete response; the best response possible was stable disease.

MGMT promoter methylation status was assessed with two distinct methylation-specific PCR assays. Only tissue samples with histologically estimated tumour-cell content of at least 80% underwent molecular analysis. DNA was extracted from paraffin-embedded tumour tissue with the DNeasy blood and tissue kit (Qiagen, Hilden, Germany). The EZ DNA Methylation-Gold Kit (HIS Diagnostics, Freiburg, Germany) was used to treat DNA with sodium bisulphite (200 ng per tumour). A172 glioma cells were used as a positive control for unmethylated tumour. Quantitative testing on real-time PCR of 182 samples was done at MDxHealth, Liège, Belgium. The same samples, along with 70 stereotactic-biopsy samples, were assessed by conventional methylation-specific PCR at the Brain Tumour Reference Centre. For discrepant results (detected in four samples, twice in each direction), the results from MDxHealth were used.

### Statistical analysis

Minimum follow-up was 12 months. The primary endpoint was overall survival, measured in days from surgery to death. Secondary efficacy endpoints included event-free survival (EFS), best response, health-related quality of life, and safety. EFS was defined as the time from surgery to first progression for patients whose disease progressed, or to death for patients without progression. Patients without progression who were alive at the end of the study were censored at the day of the last contact. Univariate descriptive analysis of overall survival and EFS was done with Kaplan-Meier estimates and a Cox’s proportional hazards model to estimate hazard ratios (HRs) and medians, both with two-sided 95% CI. To test for non-inferiority of temozolomide, we...
Table terminology criteria for adverse events (version 3.0) grades.

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<tr>
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<th>Radiotherapy (n=178)</th>
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Table 2: Numbers of grade 2–4 adverse events

used a one-sided logrank test with a tolerance level of –25% difference (radiotherapy group–temozolomide group) in median overall survival and EFS. Non-inferiority was tested with the Wellek test procedure. Only overall survival was assessed for confirmatory analysis. In view of the non-inferiority hypotheses being based on hazard ratios, we decided to apply a one-sided significance threshold of 0·05.

The best responses in the two treatment groups were compared with Wilcoxon’s test. For multivariate analysis of overall survival and EFS, we used Cox’s proportional hazards models to adjust for the following prespecified confounding factors or variables that altered the therapeutic effect: resection status (complete vs incomplete vs biopsy), histological tumour type (anaplastic astrocytoma vs glioblastoma), age in years, and MGMT promoter methylation status.

Items on the two questionnaires for health-related quality of life were scaled and scored by standard EORTC procedures. We selected eight scales for the primary analyses: emotional function, social function, overall health-related quality of life, fatigue, nausea and vomiting, loss of appetite, communication deficit, and future uncertainty. A mixed-model approach was used to estimate differences in health-related quality of life between the treatment groups. All patients with at least one valid quality-of-life assessment were included in the analyses. Because missing data and deaths are confounders for the interpretation of scores for health-related quality of life, we analysed patients in two groups according to survival status (survival for at least 3 months, at least 6 months, and at least 12 months) with the fully conditional pattern-mixture approach.

All analyses of the primary and secondary efficacy endpoints were based on all randomised patients except those who withdrew consent for data analysis or who received no dose of either trial medication after randomisation (ie, the intention-to-treat population). The per-protocol analysis of the primary endpoint included only patients without major protocol violations. The safety analyses are reported for the same population as the efficacy endpoints.

We calculated the sample size of the trial on the basis of the primary endpoint and the non-inferiority hypothesis, with an equivalence or non-inferiority limit of –53 days (–25%) of an assumed median overall survival of 7 months at a one-sided significance level of 5%, a recruitment duration of 48 months, and a dropout rate of 11%. Thus, we anticipated that 412 patients (206 in each group) would be sufficient to achieve at least 80% power.

We did all analyses with SAS (version 9.1.3) with an α error of 5%. All data were documented via remote data entry systems and held by Alcedis during the study. Alcedis also monitored the data quality.

This trial is registered with ClinicalTrials.gov, number NCT01502241.

Role of the funding source

The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the study report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 584 patients screened, 412 were eligible for enrolment (figure 1). 39 patients were excluded after randomisation and, therefore, the analysis population for efficacy endpoints (received at least one dose of dose-dense temozolomide or one fraction of radiotherapy) consisted of 373 patients. Central review of disease revealed that 40 (11%) patients had anaplastic astrocytoma and 331 (89%) had glioblastoma. The per-protocol population consisted of 362 patients, after 11 patients were excluded for protocol violations (figure 1). 39 patients were excluded after protocol violations (figure 1). Some patients had Karnofsky performance scores lower than 60, but we did not judge this deviation to be relevant for exclusion from the per-protocol population. The characteristics of patients in the two treatment groups were well balanced, although steroids were used slightly more in the radiotherapy group than in the temozolomide group during treatment (table 1).

149 (76%) patients in the temozolomide group completed at least four cycles (8 weeks) of chemotherapy (median five, range 0–20), and 149 (84%) patients completed radiotherapy. Most patients tolerated treatment well. No grade 5 adverse events were reported. Grade 2–4 adverse events were more frequent in the temozolomide group than in the radiotherapy group in all categories except for cutaneous adverse events (table 2). The main reasons for discontinuation of radiotherapy were disease progression (n=10) and sustained infection (n=8), and for
discontinuation of temozolomide were disease progression (n=141) and toxic effects (n=28).

After a minimum follow-up of 12 months after the last patient had been randomised (median follow-up from start of study 25·2 months, range 20·0 to not reached), 228 patients had died: 121 in the temozolomide group and 107 in the radiotherapy group. Overall survival at 6 months was 66·7% (95% CI 60·0–73·0) in the temozolomide group and 71·7% (65·0–78·4) in the radiotherapy group, and at 1 year, it was 34·4% (27·6–41·4) in the temozolomide group and 37·4% (30·1–44·7) in the radiotherapy group.

Median overall survival was 8·6 months (95% CI 7·3–10·2) in the temozolomide group and 9·6 months (95% CI 7·3–10·2) in the radiotherapy group. At 1 year, it was 34·4% (27·6–41·4) in the temozolomide group and 37·4% (30·1–44·7) in the radiotherapy group.

Among the 141 patients in the temozolomide group and 106 in the radiotherapy group in whom disease progression was seen, 88 (62%) and 74 (70%), respectively, received salvage therapy (p=0·227), which mainly consisted of radiotherapy in the temozolomide group and 9·6 months (95% CI 7·3–10·2) in the temozolomide group and 9·6 months (95% CI 7·3–10·2) in the radiotherapy group. Median overall survival was 8·6 months (95% CI 7·3–10·2) in the temozolomide group and 9·6 months (95% CI 7·3–10·2) in the radiotherapy group.

Disease progression or death occurred within 12 months of surgery in 325 patients (169 in the temozolomide group and 156 in the radiotherapy group). No pseudoprogressions were seen. EFS at 6 months was 30·1% (95% CI 23·6–36·6) in the temozolomide group and 35·1% (28·0–42·3) in the radiotherapy group, and at 1 year it was 12·0% (7·9–17·1) in the temozolomide group and 19·3% (14·1–25·2) in the radiotherapy group. Median EFS was 3·3 months (95% CI 2·4–4·1) in the temozolomide group and 4·7 months (4·2–5·2) in the radiotherapy group (HR 1·15, 95% CI 0·92–1·43, p=0·041).

EFS at 6 months was 30·1% (95% CI 23·6–36·6) in the temozolomide group and 35·1% (28·0–42·3) in the radiotherapy group, and at 1 year it was 12·0% (7·9–17·1) in the temozolomide group and 19·3% (14·1–25·2) in the radiotherapy group. Median EFS was 3·3 months (95% CI 2·4–4·1) in the temozolomide group and 4·7 months (4·2–5·2) in the radiotherapy group (HR 1·15, 95% CI 0·92–1·43, p=0·041; figure 2), which indicates that temozolomide was non-inferior to radiotherapy. Non-inferiority of temozolomide was also demonstrated in the per-protocol population (Pnon-inferiority=0·028).

Among the 141 patients in the temozolomide group and 106 in the radiotherapy group in whom disease progression was seen, 88 (62%) and 74 (70%), respectively, received salvage therapy (p=0·227), which mainly consisted of radiotherapy in the temozolomide group and vice versa (appendix). The likelihood of second surgery was higher in the temozolomide group than in the radiotherapy group, but not significantly so (relative risk 1·6, 95% CI 0·9–2·9, p=0·102). The likelihood of receiving salvage therapy did not differ between groups by MGMT promoter methylation status (data not shown).

Data on MGMT promoter methylation status was available in 209 patients (table 1). The baseline characteristics of these patients were similar to those of the 164 patients without MGMT promoter methylation data and were deemed representative of the population included in the efficacy analyses (data not shown). MGMT promoter methylation was detected in 73 (35%) of 209 patients (table 1). This frequency was similar to that found in the stereotactic-biopsy samples (20 [34%] of 59 conclusive results). The results in the stereotactic-biopsy samples resembled those for study tests overall (data not shown). MGMT promoter methylation was associated with longer overall survival (median 11·9 months [95% CI 9·0 to not reached] vs 8·2 months [7·0–10·0]; HR 0·62, 95% CI 0·42–0·91, p=0·014) and EFS (median 5·7 months [5·0–7·4] vs 3·5 months [3·3–3·7]; HR 0·50, 0·36–0·68; p<0·0001) than was unmethylated status (figure 3).

Extent of resection (complete vs incomplete vs biopsy) was an independent prognostic factor for overall survival in the multivariate Cox’s analysis (table 3). Tumour MGMT promoter methylation was not significant in the multivariate analysis (table 3), but was in the univariate analysis (figure 3). Age, as a continuous variable or dichotomised at age 70 years, and histology (anaplastic astrocyte vs glioblastoma) were not independent prognostic factors (table 3). We found an interaction between MGMT promoter methylation status (methylated vs unmethylated) and treatment (table 3, figure 3). Similar results were found for EFS (table 3, figure 3).

MGMT promoter methylation was associated with improved EFS in the temozolomide group, where median EFS for patients with a methylated MGMT promoter was 8·4 months (95% CI 5·5–11·7) compared with 3·3 months
Overall survival. Event-free survival. HR=hazard ratio.

Figure

Number at risk

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A

100

90

80

70

60

50

40

30

20

10

0

100

90

80

70

60

50

40

30

20

10

0

HR 0.62 (95% CI 0.42–0.91), p=0.014

B

HR 0.5 (95% CI 0.36–0.68), p<0.0001

12 months (p=0.002).

Discussion

We have shown that temozolomide alone is non-inferior to radiotherapy alone as treatment for newly diagnosed malignant gliomas in elderly patients. MGMT promoter methylation status seems to be a relevant biomarker to indicate patients who might be undertreated with radiotherapy alone. Temozolomide could, therefore, broaden the spectrum of treatment available for the increasing population of elderly patients with malignant gliomas.

The current standard care for anaplastic astrocytoma or glioblastoma in elderly patients is surgery or biopsy. Although radiotherapy alone is better than supportive care and does not reduce quality of life in elderly patients with glioblastoma, age can be a risk factor for cognitive side-effects of cranial irradiation. For evidence for such cognitive side-effects, however, is only available from non-elderly patients with irradiated low-grade tumours. A risk of decline in cognitive functioning with radiotherapy, however, should not be included in the decision-making process. Our data and those in a previously published trial do not show this effect to be relevant (table 1, appendix).

Table 3: Prognostic and predictive factors for overall and event-free survival with temozolomide on multivariate Cox's regression analysis

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<td>Temozolomide group, methylated</td>
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<td>Temozolomide group, unmethylated</td>
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Table 3: Prognostic and predictive factors for overall and event-free survival with temozolomide on multivariate Cox's regression analysis

*Status unavailable for one patient. †Data available for 209 patients. ‡Reference.
Whether the addition of chemotherapy to radiotherapy will improve outcomes in the elderly is currently being explored, but many elderly patients do not even receive chemotherapy at recurrence.\(^2\) To challenge this current practice, new trial data are needed. In a study of patients older than 70 years, including those with Karnofsky performance scores lower than 70, benefits were seen for temozolomide alone in comparison with historical controls.\(^2\) Our findings support the use of dose-dense temozolomide as an alternative option to radiotherapy alone in patients aged at least 65 years, even if followed by radiotherapy as salvage (panel). In view of the limited life expectancy in these patients, dose-dense temozolomide might be particularly useful for those without easy access to radiation oncology facilities or who prefer oral medication that can be administered and monitored close to home.

The major finding in this study is the strong predictive power of \(\text{MGMT}\) promoter methylation status for EFS: \(\text{MGMT}\) promoter methylated tumours responded better to temozolomide than radiotherapy, whereas the opposite was true for unmethylated tumours. A similar but non-significant effect was seen for overall survival; the data suggest that this finding was not due to resolving pseudoprogressions after radiotherapy, but rather to a good response to salvage temozolomide treatment. The concept of pseudoprogression was well known at all study centres and was regularly ruled out by MRI assessments repeated after short intervals. Stratification of patients by the use of one biomarker is not an established approach in neuro-oncology, despite supportive landmark data,\(^7,8\) or in general oncology. Although testing for \(\text{MGMT}\) promoter methylation poses known challenges,\(^9\) our data, in conjunction with those from the German Glioma Network,\(^2\) justify or even call for the routine testing of the \(\text{MGMT}\) promoter methylation status in elderly patients with anaplastic astrocytoma or glioblastoma. We believe this approach will improve outcomes, prevent unnecessary toxic effects, and save money.

Limitations of the NOA-08 study were weaknesses inherent to a non-inferiority design, the selection of a generous tolerance level, a one-sided test procedure, and possible non-proportional hazards for EFS. Only 56% of tissue samples available for \(\text{MGMT}\) testing showed conclusive results, mainly because of the high percentage collected during stereotactic biopsies, which can yield limited amounts of tumour DNA owing to small specimen sizes. The results from the stereotactic-biopsy samples were, however, deemed to be representative of those for the efficacy analysis population in all relevant aspects.

Although temozolomide was associated with haematological toxic effects, raised liver-enzyme concentrations, asthenia and fatigue, and gastrointestinal side-effects in a notable number of patients, few were grade 4 adverse events (table 2). The events might be due to the dose-dense schedule and particularly careful monitoring owing to the age of the patients, in whom even grade 2 adverse events can affect quality of life. In another trial, dose intensification in the adjuvant setting of primary combined modality treatment was not associated with increased overall survival in patients younger than 65 years who had glioblastoma.\(^2\) Likewise, no differences were seen between patients with methylated and unmethylated \(\text{MGMT}\) promoter status.\(^2\) Thus, temozolomide alone administered according to a conventional schedule might also be useful in elderly patients who have malignant glioma with positive...
The ANOCEF trial\(^1\) showed that radiotherapy was better than supportive care in elderly patients (older than 70 years) who had glioblastoma. The EORTC 26981/22981 NCIC CE.3 trial (NCT00482677)\(^7,8,10\) indicated that MGMT promoter methylation predicts sensitivity to alkylating agents in glioblastoma. Our findings that treatment with temozolomide alone is non-inferior to radiotherapy alone, therefore, adds a new option to the care of newly diagnosed malignant gliomas in elderly patients. More importantly, our trial identified MGMT promoter methylation status as a predictive biomarker for event-free survival, and our findings suggest that elderly patients with methylated tumour MGMT promoter status should not be treated with radiotherapy alone, as is currently done for most patients, but should receive temozolomide alone or in combination with radiotherapy if the EORTC and NCIC trial is positive. Further testing of MGMT promoter methylation status warranted assessment in this patient group.

**Interpretation**

**Systematic review**

We searched ClinicalTrials.gov, Google, and PubMed for current, reported, or published single-arm or randomised phase 2 and 3 trials involving elderly patients (age older than 60 years) with malignant gliomas. We used the search terms “glioma,” “anaplastic,” “glioblastoma,” “astrocytoma,” “radiotherapy,” “chemotherapy,” “resection,” “temozolomide,” “dose-dense temozolomide,” “older,” “elderly,” “trial,” and “study.” We also searched for any evidence on molecular biomarkers being used for decision-making in gliomas. Search terms were “biomarker,” “prognosis,” “prediction,” and “MGMT.” From these searches we were confident that dose-dense temozolomide alone would not be inferior to radiotherapy alone in the management of newly diagnosed anaplastic astrocytoma or glioblastoma in elderly patients (age older than 65 years) and that MGMT promoter methylation status warranted assessment in this patient group.

MGMT promoter methylated status and could be associated with reduced risk of toxic effects. However, when this trial was designed and undertaken, no comparative data for different temozolomide schedules were available. One study had reported efficacy with a dose-dense schedule of temozolomide;\(^6,29\) but when it was compared with radiotherapy in patients with glioblastoma, superiority of temozolomide was not shown.\(^6,29\) Similarly, information on the potential non-inferiority of short courses of radiotherapy compared with longer courses was only emerging when NOA-08 had already been designed.\(^6,29\)

The cut-off age of 65 years for elderly patients is a controversial issue in neuro-oncology, and is arbitrary in some patients.\(^7\) While the threshold might shift towards 70 years in the studies of glioblastoma, it is likely to be closer to 60 years in those of primary brain lymphoma, where more aggressive treatments are explored. Other factors, such as neurological function or comorbidities are relevant, while in a trial cohort with good general health, such as the NOA-08 trial population, age alone is not prognostic.

We propose that future research efforts should explore the biological basis underlying the poor outcome associated with gliomas in the elderly to find an alternative to age as a basis for clinical decision-making. IDH1 mutations have been identified as specific positive prognostic markers for gliomas in patients younger than 65 years.\(^4,31\) Anaplastic astrocytoma in the elderly and primary glioblastoma typically lack IDH1 mutations but show similar unfavourable outcomes.\(^3,4\) This difference justified the inclusion of patients with anaplastic astrocytoma in this trial as well as our focus on MGMT but not IDH1. In the small number of patients with anaplastic astrocytoma included, however, we found that both treatments were efficacious, although the results were worse than those for younger patients with anaplastic astrocytoma in previous trials.\(^3,31\) In that respect, in patients who have the IDH-associated glioma and MGMT promoter methylation,\(^11\) the predictive properties of MGMT promoter methylation status might be diluted, which could explain why MGMT is not predictive for outcomes in younger patients with anaplastic gliomas.\(^30\)

We feel our findings have the potential to change practice for the treatment of elderly patients with anaplastic astrocytoma or glioblastoma. We expect our observations to be confirmed in the Nordic trial, as the researchers have previously reported similar efficacy for radiotherapy alone and temozolomide alone, albeit with a different temozolomide regimen (treatment on 5 of 28 days) and in younger patients (age 61 years or older) with glioblastoma only.\(^28\) Importantly, we have defined MGMT promoter methylation as a predictive biomarker that could help to guide clinicians to decide between radiotherapy and temozolomide. As a complementary approach and as a next step of standardising treatment of elderly patients with gliomas, the joint study of the National Cancer Institute of Canada and the EORTC is exploring the efficacy of radiotherapy alone versus radiotherapy plus temozolomide (NCT00482677). Our findings should provoke discussion in relation to patients with positive MGMT promoter methylation status in the radiotherapy standard care arm, especially as these patients show no more benefit from salvage temozolomide than do patients with unmethylated status. Data from that study could further validate the role of MGMT as a predictive biomarker in elderly patients and confirm that temozolomide produces no benefit in patients with unmethylated tumours. A positive outcome should provoke discussion of whether temozolomide alone, with radiotherapy only as salvage, could be a sufficient treatment for patients with MGMT promoter methylated tumours.

**Contributors**

WW and MW conceived the trial in collaboration with the German Neuro-oncology Working Group of the German Cancer Society. WW reviewed the data. CM did the statistical analysis. JF and GR reviewed the histological specimens and analysed the MGMT promoter methylation status. The article was written by WW and MW, with support from MP, CM, JF, GT, MS, GN, KP, JPS, MS, SEC, JV, CB, JM, RR, RM-S, and GR. The paper was reviewed and approved by all authors.

**Conflicts of interest**

WW, JPS, GR, and MW have received consulting and lecture fees, and WW and MW have received research support from Merck Sharp & Dohme. The other authors declare that they have no conflicts of interest.

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