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Adjuvant dibromodulcitol and BCNU chemotherapy in anaplastic astrocytoma: Results of a randomised European Organisation for Research and Treatment of Cancer phase III study (EORTC study 26882)

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ABSTRACT

Background: In a previous randomised EORTC study on adjuvant dibromodulcitol (DBD) and bichloroethylnitrosourea (BCNU) in adults with glioblastoma multiforme (GBM) and anaplastic astrocytoma (AA), a clinically significant trend towards a longer overall survival (OS) and a progression-free survival (PFS) was observed in the subgroup of AA. The aim of the present study was to test this adjuvant regimen in a larger number of AA patients.
Methods: Continuation of the previous phase III trial for newly diagnosed AA according to the local pathologist. Patients were randomised to either radiotherapy only or to radiotherapy in combination with BCNU on day 2 and weekly DBD, followed by adjuvant DBD and BCNU in cycles of six weeks for a maximum total treatment duration of one year. OS was the primary end-point.
Results: Patients (193) with newly diagnosed AA according to local pathological assessment were randomised to radiotherapy (RT) alone ($n = 99$), or to RT plus DBD/BCNU ($n = 94$); 12 patients were considered not eligible. At central pathology review, over half (53%) of the locally diagnosed AA cases could not be confirmed. On intent-to-treat analysis, no statistically significant differences in OS ($p = 0.111$) and PFS ($p = 0.087$) were observed, median OS after RT was only 23.9 months 95% confidence interval (CI), [18.4–34.0] after RT plus DBD/BCNU 27.3 months 95% CI [21.4–46.8].
Conclusion: No statistically significant improvement in survival was observed after BCNU/DBD adjuvant chemotherapy in AA patients. The trend towards improved survival is consistent with previous reports. Central pathology review of grade 3 tumours remains crucial.

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1. Introduction

The benefit of adjuvant chemotherapy in addition to radiotherapy in high-grade glioma has been controversial for many decades. A large meta-analysis based on individual patient data from 12 randomised trials including 3004 patients suggests a statistically significant benefit of adjuvant chemotherapy in malignant glioma.[1] This analysis found an absolute survival increase of 5% at two years with the administration of adjuvant chemotherapy. In this meta-analysis the observed benefit was comparable in patients with anaplastic astrocytoma (AA) and with glioblastoma multiforme (GBM) patients. The results of a previous EORTC study (EORTC 26882, ClinicalTrials.gov number, NCT00002620), initiated in 1988 and reported in 1994 suggested that adjuvant dibromodulcitol (DBD) during and after radiotherapy in combination with BCNU is an effective adjuvant therapy in malignant gliomas.[2] In this study it appeared that in particular in AA patients survival was increased after treatment with BCNU and DBD, and less so in patients with GBM. However, the number of patients in the AA subgroup was too small to reach statistical significance. Therefore, this study was amended and reopened to accrual in 1994 for AA patients only. The results of this extended cohort of AA patients as diagnosed by the local pathologist during the entire conduct of the trial are the subject of this report.

2. Methods

2.1. Patients

Eligibility criteria for this study were age older than 15 years; MRC neurologic function status 3 or less (moderate neurologic symptoms and less than fully active; or better), expected survival longer than eight weeks; normal blood, renal and hepatic function; absence of major concurrent illness. In the initial study all high grade glioma according to the WHO classification were eligible, following the re-opening only patients with AA were eligible.[2] The inclusion was based on the diagnosis made by the local pathologist with a central pathology review being part of the study. The study was approved by the Institutional Review Boards of all participating institutions.

2.2. Treatment

Patients were randomised to either radiation therapy alone (RT, group 1), or to a combination of RT and DBD plus BCNU (group 2). RT was given a dosage of 60 Gy in daily fractions of 1.8–2.0 Gy to the enhancing tumour volume using the pre-operative CT or MR scan plus a margin of 2–3 cm. DBD was given during RT at a dosage of 700 mg/m^2 on days 1, 8, 15, 22, 29 and 35. Maintenance chemotherapy after RT consisted of DBD 1000 mg/m^2 on day 1, and BCNU 130 mg/m^2 i.v. on day 2, given every six weeks until tumour progression but for no longer than one year. Drug dose intensity (DI) was calculated by dividing the total actual given dose by the total treatment duration. The percentage of relative dose intensity was obtained by dividing the observed DI by the scheduled DI.

2.3. Statistical considerations

Patients were randomised centrally at the EORTC Data Centre by using telephone. At randomization, patients were stratified by institution and surgery type: biopsy versus tumour resection. The original trial design from 1988 included both grade 3 and grade 4 gliomas. The anticipated median overall survival in group 1 (RT only) was 12 months. A total of 192 deaths out of a sample size of 212 patients were required to detect six month increase in the median overall survival (Hazard ratio (HR) = 0.667) based on a two-sided log rank test at significance level of 5% with a power of 80%. The trial was reopened in 1994 for AA only using the same statistical assumptions, aiming at 212 AA patients.

Overall survival (OS) was defined as the time interval between the date of randomization and the date of death. Progression free survival (PFS) was defined as the interval between the date of randomization and the date of progression or death, whichever would occur first. Progression was defined as the neurological deterioration of at least one symptom, the appearance of increased intracranial pressure or a 50% increase of the tumour size on a contrast enhanced CT scan (and later MR scan). OS and PFS were calculated according to the Kaplan Meier method. Treatment comparisons were made with two-sided log rank tests. The Cox proportional hazards model was fitted to adjust the treatment effect for the extent of surgery (biopsy versus resection), age ($\leqslant$40 versus >40), post-surgical WHO Performance Status score, and the period of randomization (<1994 versus $\geqslant$1994). The analysis was based on the diagnosis of AA made by local pathologists (intent-to-treat analysis).

3. Results

In the entire study a total of 418 patients were included. The present analysis describes the outcome in the predetermined subgroup of 193 patients diagnosed with an AA by the local pathologist. Preliminary results on the first 58 AA patients and the cohort of patients with glioblastoma were previously reported.[2] After the reactivation of the study in December 1994 an additional 148 patients were enrolled in the amended study: 135 with AA according to the local pathologist and 13 with ineligible histologies (GBM). The trial was closed for enrollment in June 2000, a few patients short of reaching the intended 212 AA patients because of a decreasing accrual rate. Ninety-nine of the eligible 193 AA patients were randomised to RT alone and 94 to RT plus DBD/BCNU; 191 AA patients were considered eligible (98 in the RT and 93 in the DBD/BCNU arm). The main reason for not meeting the eligibility criteria was the poor performance status. Patients (181) were treated and included in the safety analyses (94 in the RT arm and 87 in the DBD/BCNU arm; see Fig. 1 for a CONSORT flow diagram). The main reasons for excluding 12 patients were treatment refusal (n = 6) and severe protocol violations (n = 3). Table 1 summarises the main post-surgical patient characteristics of the two groups; no significant differences were observed between these groups. After 152 events an Independent Data Monitoring Committee reviewed the data in May 2005; they recommended a full analysis and publication of the results.

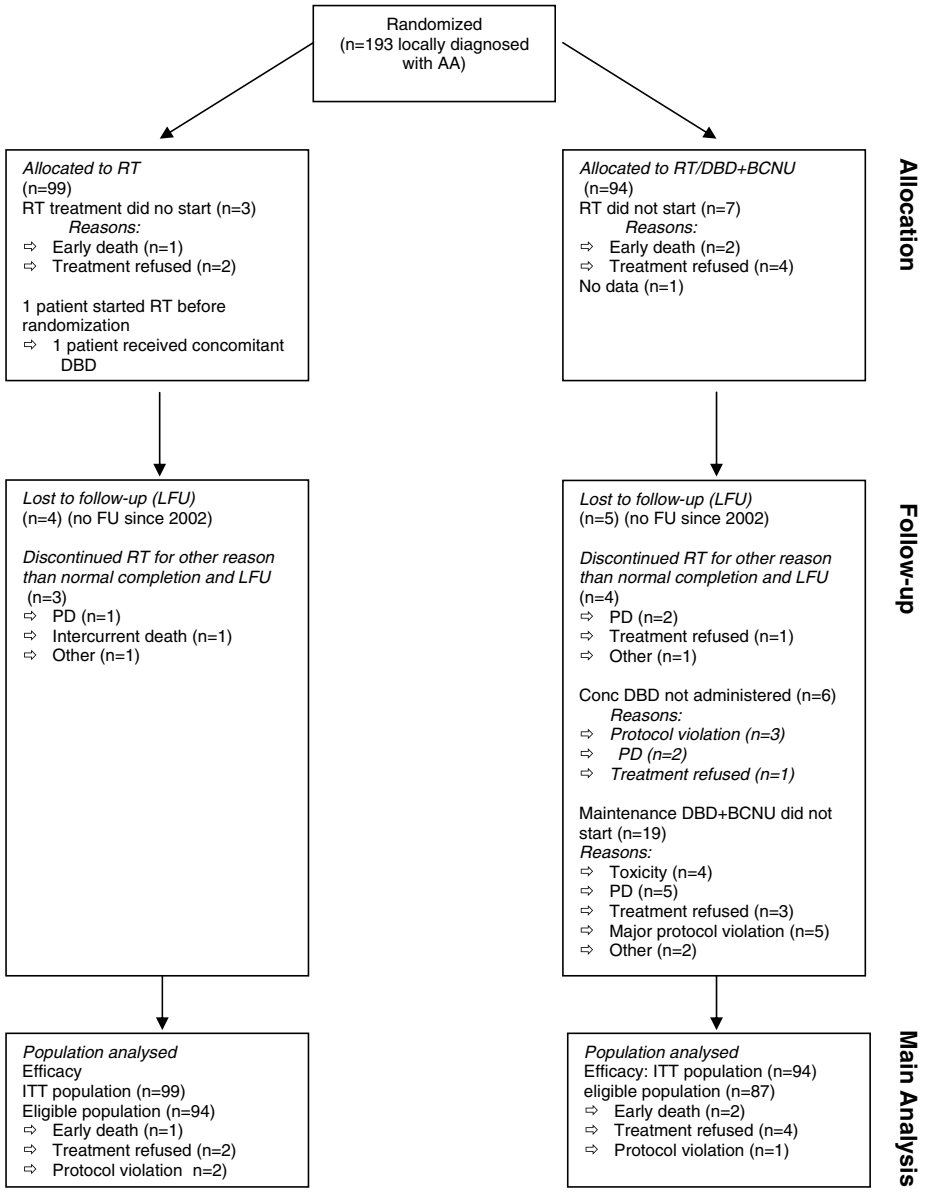

Fig. 1 – CONSORT flow diagram with the numbers of patients randomised and treated.

3.1. *Pathology review*

Of the 193 AA diagnosed by the local pathologist, 176 were available for review by the central pathologist. At review, 61 (35%) patients were diagnosed with an AA, 13 (8%) with an anaplastic oligoastrocytoma (AOA), 4 (2%) with an anaplastic oligodendroglioma (AOD), 44 (25%) with a GBM, 41 (23%) with a low grade glioma, 13 (7%) with another diagnosis.

3.2. *Treatment*

RT was started in 94 patients of group 1 and 87 of group 2 (Table 2). The median interval between surgery and radiotherapy was seven weeks. The complete scheduled RT dose of 60 Gy (±2 Gy) in 30 daily fractions was delivered to 89 patients (95%) of group 1, and 81 (93%) of group 2. The main reasons for early RT discontinuation were tumour progression ($n = 4$), death due to intercurrent pulmonary disease ($n = 1$), patient's refusal ($n = 1$) and blindness ($n = 1$).

Concomitant DBD was started in 81 patients (93%) of group 2. The reasons for not starting DBD were protocol violation ($n = 3$), disease progression ($n = 2$), and treatment refusal ($n = 1$).

Two-thirds of the patients received 90% or more of the scheduled concomitant DBD-dose. Maintenance DBD/BCNU chemotherapy was given to 68 patients (72%) of group 2. The main reasons for not giving the maintenance therapy were disease progression ($n = 5$), protocol violation ($n = 5$), toxicity ($n = 4$) and treatment refusal ($n = 3$). The number of cycles and the relative DI for both drugs are given in Table 2. In summary, 36 of 87 group-2 patients (41%) received at least six cycles of adjuvant chemotherapy. The main reasons for early treatment discontinuation were tumour progression ($n = 19\%$ or 22%), treatment toxicity ($n = 13\%$ or 15%), patient's refusal

Table 1 – Post-surgical characteristics of the 193 anaplastic astrocytoma patients as diagnosed by the local pathologist

Patient characteristics	Group 1: radiotherapy	Group 2: RT + DBD/BCNU
No. of patients included	99	94
No. of patients eligible	94	87
Male (%)	56	59
Median age, yrs (range)	40 (19–79)	44 (24–74)
Median time from 1st symptom to randomization (mo)	3.1 (0.4–163)	2.3 (24–74)
Normal consciousness (%)	98	97
Median Karnovsky score	90	90
Post-surgical WHO-PS grade (%)		
0	23	25
1	59	50
2	17	17
3	1	2
Unknown	–	6
Type of surgery (%)		
Biopsy	25	27
Partial resection	24	25
Grossly total resection	51	48
Corticosteroids administration (%)		
Yes	17	22
No	78	72
Not reported	5	5

Table 2 – Administered treatment and dose-intensity in both treatment arms

Treatment	Group 1: radiotherapy	Group 2: RT + DBD/BCNU
Radiotherapy		
No. of eligible patients randomised	99	94
No. of patients treated	94	87
Median dose in Gy (range)	59.6 (1.9–66)	60 (2–61.7)
Median no. of fractions (range)	30 (6–33)	30 (1–36)
Median duration in weeks (range)	6.3 (1–9.3)	6 (0.1–11.3)
Median target volume in cm^3 (range)	259 (18–999)	275 (9–1272)
Median treatment volume in cm^3 (range)	462 (24–2700)	480 (80–1632)
DBD during radiotherapy		
Median relative dose intensity (range)	–	94% (16–137)
DBD + BCNU following radio therapy		
No. of cycles: median (range)	–	6 (1–10)
No. of patients who completed 6 cycles (%)	–	36 (38)
Median relative DBD-dose intensity (range)	–	93% (56–142)
Median relative BCNU-dose intensity (range)	–	92% (44–124)

to continue chemotherapy (n = 7% or 8%), and protocol violation (n = 6% or 7%).

3.3. *Outcome*

At the time of this analysis, 152 of the 193 AA patients (79%) had died. In 127 patients (82%) death was attributed to tumour progression and in 3 patients to radiation necrosis/progressive deterioration. Six patients died from pulmonary embolism or infection. In six patients the cause of death was unrelated to disease or treatment, in 10 the cause of death was either uncertain or not reported at all. In the intent-to-treat population, median survival was 27.3 months after RT with DBD/BCNU 95% Confidence Interval (95% CI) [21.4;46.8] and 23.9 months after RT (95% CI: [18.4;34.0]; Unadjusted HR [95% CI] RT/DBD + BCNU versus RT was 0.77 [0.56;1.06] HR was 0.75 [0.54;1.04] after adjustment in a Cox model, Fig. 2 and Table 3). Similarly, progression-free survival showed a trend in favour of the chemotherapy arm (12.4 months [9.2;15.0] versus 14.8 months [11.9;19.5]), again not reaching statistical significance.

3.4. *Toxicity*

The main toxicity attributed to chemotherapy was myelosuppression (Table 4), which either caused dose reduction or administration delay of DBD or BCNU in 13% of 322 maintenance cycles. During RT, in the chemotherapy arm five patients (6%) suffered from a grade 3 or a grade 4 nausea/vomiting. No other significant toxicities were reported, and no death was attributed to chemotherapy.

4. Discussion

This trial was one of the first randomised phase III studies investigating AA only, and (to the best of our knowledge) is still the only randomised controlled trial on adjuvant chemotherapy in AA with a radiotherapy only control arm.[3,4] DBD is an alkylating agent, causing single-strand DNA breaks.[5] If given together with BCNU it appeared to potentiate BCNU cytotoxicity.[6] It has a good penetration over the blood brain barrier, and in combination with BCNU showed an interesting activity in early studies on newly diagnosed high grade glioma.[7,8] The trend towards a longer OS (difference in median survival 3.5 months) and PFS (difference in PFS of 2.4 months) observed in the present study after treatment with adjuvant DBD plus BCNU did not reach statistical significance, however. At two years, 56% of patients in the experimental arm were still alive, versus 49% in the control arm. The study was prematurely closed because of decreasing accrual. In addition, the observed survival in this study was also markedly longer than expected, even in the control arm. In view of these developments the Independent Data Monitoring

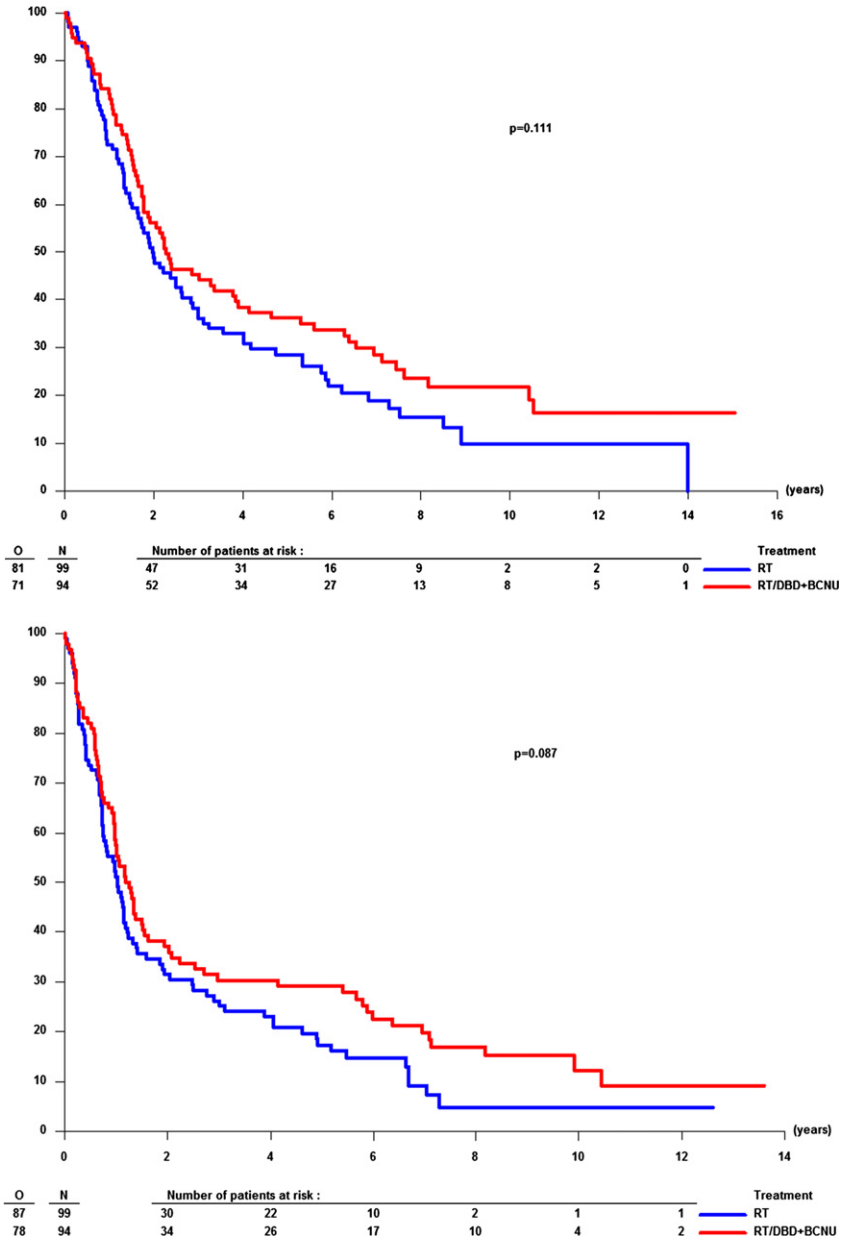

Fig. 2 – Kaplan–Meyer estimate of the overall survival (OS, upper panel) and progression free survival (PFS, lower panel) in 193 patients with grade 3 glioma diagnosed by local pathologist. OS and PFS in 99 patients randomised to receive RT alone is compared to 94 patients randomised to be treated by RT plus DBD/BCNU. The difference does not reach the level of significance neither for OS ($p = 0.111$) nor for PFS ($p = 0.087$).

Committee recommended that the results should be analysed even though the number of observed events was still lower than the required number of events. The lower number of events has impacted on the power of the study. Based on the actual observed total number of events (152), this study had a 50% power to detect an increase of 50% in median survival (which corresponds to a 'risk of death' decrease of 33% or a Hazard Ratio of 0.67).

The MRC meta-analysis of adjuvant chemotherapy in high-grade glioma observed a two-year survival of 31% in the radiotherapy group and 37% in the chemotherapy group in AA patients.[1] In comparison, the present study shows an overall better two-year survival but with a similar increase in two-year survival in the chemotherapy arm compared to treatment with radiotherapy only. Thus, the outcome of the present study is in agreement with the findings of the MRC meta-analysis, which showed that adjuvant chemotherapy confers a small overall survival benefit (5% increase at two years) in high-grade glioma. This result was achieved with a treatment that was in general well tolerated. The most frequent side effect was a reversible myelosuppression (grade 3 or 4 in 23% of patients); no fatal toxicities were observed.

The objective of the study was to investigate the benefit of DBD/BCNU in AA patients. In the original study design the inclusion was based on the 1979 WHO criteria for brain tumours.[9] In 1993 and 2000, revisions of the WHO criteria for

Table 3 – Overall Survival median, 1-year and 5-year survival in both treatment arms

Survival	Treatment	
	Radiotherapy	Radiotherapy/DBD + BCNU
Median [95% CI] (months)	23.9 [18.4;34.0]	27.3 [21.4;46.8]
12 months survival rate [95% CI] (%)	72.5 [63.6;81.3]	83.0 [75.4;90.6]
24 months survival rate [95% CI] (%)	48.8 [38.5;58.2]	56.1 [45.5;65.5]
60 months survival rate [95% CI] (%)	28.6 [19.5;37.7]	36.2 [26.3;46.1]

Table 4 – Grade 3 or 4 haematological toxicity related to chemotherapy

Toxicity	DBD during radiotherapy	Adjuvant DBD + BCNU	Entire study
	(n = 87)	(n = 68)	(n = 87)
Leukopenia	4 (5%)	9 (13%)	11 (13%)
Neutropenia	7 (8%)	5 (7%)	7 (8%)
Thrombocytopenia	2 (2%)	14 (20%)	14 (16%)
Anemia	1 (1%)	1 (1%)	1 (1%)
Any grade 3 or 4	8 (9%)	16 (23%)	20 (23%)

the histopathological diagnosis were published.[10,11] The past decade also showed a trend towards a more frequent diagnosing of oligodendroglial tumours, due to changing criteria and eagerness for this diagnosis.[12,13] These changes may have been a factor in the decreasing accrual of the present study. Unfortunately, both the classification and the grading of these tumours are rather subjective, which does contribute to the large interobserver variation in the diagnosis of AA.[14] The present study underscores this, with a central confirmation of the diagnosis "AA" in only one third of the cases. The interobserver variation in studies on grade III tumours is in general much larger than what has been reported in studies on GBM.[3,12,15,16] A central pathology review prior to study entry would have prevented these cases from entry into the study, but it is not clear what clinical conclusions could have been drawn from that design. The present trial design was based on the local pathology diagnosis, which is in fact the 'real life' situation: in every day clinical practice patients are being treated based on a local diagnosis, and not on a central pathology review or on a consensus diagnosis. Clearly, more objective and reproducible criteria for the diagnosis of grade III astrocytic tumours are needed.

What is currently the role of adjuvant chemotherapy in grade III glial tumours? This has become an important question, in particular after the randomised trial that observed a survival benefit of combined chemo-irradiation with temozolomide in GBM.[17] This result is in contrast with the outcome of two trials on adjuvant PCV chemotherapy in anaplastic oligodendroglial tumours, which tumour type is generally considered to be more sensitive to chemotherapy as compared to anaplastic astrocytoma (especially in the presence of combined 1p/19q loss).[18,19] In both trials (neo-) adjuvant PCV improved progression free survival but not overall survival, probably because most patients in the radiotherapy control arm received (PCV-) chemotherapy at progression. The major conclusion of these two trials therefore is that if given sequentially with radiotherapy, the timing of chemotherapy (adjuvant or at the time of recurrence) does not impact the overall survival. Even though the temozolomide chemo-irradiation study was limited to GBM patients, there is currently a trend towards treating AA and other grade III tumours with combined chemo-irradiation. It remains speculative, however, that daily combined radiotherapy and temozolomide will also improve the outcome in grade III tumours. Moreover, many of these patients do have prolonged survival, and therefore delayed or late toxicities (e.g. delayed leukoencephalopathy, secondary malignancies) are potentially more of an issue in these patients. To address this question two large intergroup trials involving both European and North-American cooperative brain tumour groups will investigate concurrent and adjuvant chemotherapy in grade III tumours, including anaplastic oligodendrogliomas and oligoastrocytomas. Based on the recent trials that demonstrated a much better prognosis for patients with oligodendroglioma and oligoastrocytoma with co-deletions of 1p and 19q, separate trials will be conducted in tumours with and without combined 1p/19q loss.

In conclusion, this study on adjuvant chemotherapy in locally diagnosed AA patients failed to demonstrate a survival benefit in intent-to treat analysis. Nevertheless, there was a trend towards improved outcome with the addition of chemotherapy, similar to the previous meta-analysis on adjuvant chemotherapy in high-grade gliomas.

Conflict of interest statement

None declared.

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