Central nervous system tumours

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Radiotherapy for high-grade glioma: is altered fractionation beneficial?

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Purpose: The publication of RTOG 83-02 in 1996 stimulated further investigations of altered fractionation in high-grade glioma. We summarize the results of trials published between January 1997 and June 2002.

Materials and Methods: Medline search by key words: brain tumors/astrocytoma/glioma/high-grade glioma/malignant glioma/glioblastoma multiforme and accelerated radiotherapy/hyperfractionated radiotherapy/altered fractionation. In addition, the search was extended to reference lists of articles and textbooks. Whenever possible, data were extracted from the original papers on an intention-to-treat basis, i.e. patients with protocol violations were not excluded for the purpose of our analysis. Studies in brain stem glioma and children as well as studies which achieved acceleration by radiosurgery, stereotactic radiotherapy, or brachytherapy rather than conventional external beam treatment were not included.

Results: We identified 1414 patients from 21 studies, 2 of these were randomised phase III studies. Seven studies (658 patients) did not use chemotherapy or radiosensitizers in addition. The others provide a very heterogeneous set of data because a large variety of drugs and administration schedules can be found. Seven studies included patients with glioblastoma multiforme only, two were limited to patients with anaplastic glioma. Dose per fraction was 1.2-1.8 Gy in 17 studies and 1.9-2.65 Gy in 4 studies. Overall treatment time was 12-31 days, except for one study. Three out of 5 studies where 3 fractions per day were administered, included a 2-week break. None of the studies reported a significant improvement in survival by altered fractionation in comparison to either institutional historical controls or their respective randomised control arm. Doses of 60-70 Gy do not appear to improve survival compared to 50-60 Gy. The current data provide no arguments for use of 3 fractions instead of 2 fractions per day. Median survival was 10 months after radiotherapy alone (658 patients) and 11 months after combined treatment (756 patients). Regarding 2-year survival rates, radiotherapy alone resulted in 13%, combined chemoradiation or use of sensitizers in 23%. However, distribution of prognostic factors favours the combined treatment group. Evaluation of 6 studies of conventional radiotherapy alone resulted in data of 571 patients. Their median survival was 10.8 months. Cumulative 2-year survival was 15%. The studies of conventional radiotherapy plus chemotherapy or sensitizers included 1115 patients with a median survival of 11 months (2-year survival was 18.5%).

Conclusion: Altered fractionation shortens the overall treatment time for adult patients with supratentorial high-grade glioma. However, there is no significant survival improvement.

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Phase I study of OSI-774 alone or with temozolomide in patients with malignant glioma

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Purpose: To evaluate the toxicity and safety of OSI-774 alone or with temozolomide.

Methods: Adult patients (pts) with stable or recurrent malignant glioma (MG) were treated with OSI-774. Pts previously treated with temozolomide without evidence of progression, or currently on temozolomide with stable disease could also be enrolled. Pts were stratified based upon the use of enzyme-inducing antiepileptic drugs (EIAEDs). Thus, 4 cohorts of pts were treated: Pts on OSI-774 alone or OSI-774 plus temozolomide who were not on EIAEDs (Group A pts), and similar groups who were on EIAEDs (Group B pts). The dose of OSI-774 began at 100 mg/day/orally and was increased by 50 mg/day increments in cohorts of 3 pts/groups until Dose Limiting Toxicity (DLT) occurred. DLT was assessed in the first two weeks of treatment, and included any grade-3 non-hematologic or grade-4 hematologic events. If pts were treated with both agents, OSI-774 was started 7 days prior to temozolomide. The dose of temozolomide was 150 mg/m2/day x 5 for the first cycle, and could be increased to 200 mg/m2/day x 5 in subsequent cycles given every 28 days. Toxicity and pharmacokinetics (pk) were assessed as well as response for pts who were treated at the time of relapse. Pts treated with stable disease were evaluated for toxicity and pk only.

Results: 66 pts are currently enrolled, median age 57, 35 males/31 females; 55 with Glioblastoma or Gliosarcoma with the remaining with grade-3 lesions. 49 were treated at relapse and 17 with stable disease. 39 pts were treated with OSI-774 alone; 27 with the combination. The major toxicity has been grade-2 or greater rash. Diarrhea has been well controlled with loperamide. DLT has been reached for group A OSI-774 alone patients at 250 mg/day (MTD is 200 mg/day). Current dose for OSI in the remaining groups: group A OSI-774 plus temozolomide is 250 mg; group B OSI-774 alone 500 mg; group B OSI-774 plus temozolomide 350 mg. Preliminary pk results confirm that EIAEDs reduce exposure to OSI-774 and its active metabolite by 50-75%. There have been 8 partial or complete responses thus far in the 49 pts treated at relapse.

Conclusion: Toxicity is acceptable at the current doses and pk data show decreased exposure of OSI-774 and metabolites due to EIAEDs. Encouraging objective responses have occurred. Accrual is ongoing with plans for phase II.

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The TGF-beta2 antisense oligonucleotide ap 12009 as a therapeutic agent in recurrent high-grade glioma: safety and efficacy results of phase I/II clinical trials

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AP 12009 was developed to block the mRNA of TGF-beta2, which correlates with bad prognosis in high-grade glioma. TGF-beta is the most potent immunosuppressor known (Jennings MT et al., 1998). In three phase I/II dose escalation studies patients with high-grade glioma (WHO grade III and IV) have been treated intratumorally with a single course (first study), a second course (second study), or up to ten courses (third study) of the TGF-beta2 antisense oligonucleotide AP 12009. Adult patients with recurrent high-grade glioma and evidence of tumor progression on MRI were included. In total, the dose per course was escalated 113-fold. The therapy was applied by convection enhanced delivery (CED), using an indwelling pump system. Excellent safety and tolerability results were obtained in the studies: in only 6 of the total 27 patients "possibly" related adverse events were observed, mostly of grade 1 or 2. There were no changes in laboratory values, incl. hematological parameters. All doses up to the highest were considered safe as evaluated by an independent Data and Safety Monitoring Board. Application system and CED were tolerated without problems and well accepted by both physicians and patients. Thus far, the 20 patients from the first two studies have been evaluated for efficacy. While comparable median overall survival (mOS) data from literature for recurrent patients treated with the standard drug temozolomide are 42 weeks for anaplastic astrocytoma (AA), and 32 weeks for glioblastoma (GBM), the mOS in this study is 77.0 weeks for AA, and 42.4 weeks for GBM; mOS for 13 patients having received temozolomide as chemotherapy before AP 12009 is even 106.4 weeks for AA, and 46.1 weeks for GBM, respectively. 6 patients in the 1st study, and one more in the 2nd study showed at least stabilization, incl. one patient in the 1st study with complete response in all tumor sites; this patient is still alive 196.4 weeks after the recurrence (110 weeks after start of AP 12009).

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Development of glioma-like models in mice and its application in chemotherapy intervention studies

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Background: Due to the presence of the blood-brain barrier (BBB), the central nervous system is considered to be a sanctuary site for many anti-