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-

cancer drugs (e.g. paclitaxel). Our aim is to develop different experimental glioma models in mice with intact and locally disrupted BBB to study the efficacy of better treatment modalities for gliomas.

Methods: Tumor cell lines of different origin were implanted intracranially in nude mice. To allow non-invasive monitoring of tumor growth in vivo, cell lines were tagged with the firefly luciferine-gene. Tumor growth was monitored using the IVIS camera (Xenogen Inc.). Vascular leakage in the tumor (a measure for BBB properties) was detected using 7T contrast enhanced MRI with gadolinium-DTPA. Mice implanted with Mel57 cells were treated with i.v. paclitaxel at 9, 11 and 13 days after tumor cell implantation.

Results: The implantation of the different cell lines resulted in xenograft mouse models for glioma, displaying the infiltrative, invasive and expansive growth characteristics of a glioma with or without intact BBB properties (Table). Tumor growth could already be visualized 6 days after implantation of the tumor cells. The relationship between tumor mass and bioluminescence was validated using standard histological techniques. So far, we have tested the efficacy of paclitaxel against intracranial Mel57 cells and did not observe a significant decrease of tumor growth.

Cell-line	Species	Origen	Growth pattern	BBB
U-87	Human	Glioblastoma	Expansive, angiogenic	Not intact
U-118	Human	Glioblastoma	No growth	–
K1735	Murine	Melanoma	Infiltrative, co-optive	Intact
Mel57	Human	Melanoma	Invasive, co-optive	Intact
Mel57VEGF165	Human	Melanoma	Expansive, angiogenic	Not intact
SMT	Human	Melanoma	Expansive, some invasion	To be determined
MDA MB 435	Human	Breast	Expansive, angiogenic	To be determined

Conclusions: We have successfully developed several glioma models in mice. In vivo imaging by luciferase allows convenient follow-up of tumor growth for intervention studies. Paclitaxel is not effective against implanted Mel57 cells, a tumor that is protected by the BBB, and we expect that the BBB plays an important role in this inefficacy of paclitaxel. To further study the role of the BBB in the protection of brain tumors, we are currently extending our experiments in the other tumor models. Moreover, since paclitaxel is a substrate of the drug transporter P-glycoprotein (Pgp), we are also studying the effect of Pgp in the BBB using Pgp deficient mice.

Ovarian cancer

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Paclitaxel/Carboplatin (TC) vs Paclitaxel/Carboplatin sequentially followed by Topotecan (TC-Top) in first-line treatment of ovarian cancer Figo stages IIB - IV interim results of a gynaecologic cancer intergroup phase III trial of the Ago ovarian cancer study group and Gineco

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Between 12/1999 and 03/2002 1308 patients were randomized to receive 6 cycles of Paclitaxel (175 mg/m2 3h iv) and Carboplatin (AUC 5, Calvert formula) followed by surveillance (TC) or by 4 cycles of Topotecan (1.25 mg/m2 iv d1-5) (TC-Top) on a 3 weekly schedule. The primary objective was to test for superiority of TC-Top in terms of overall survival. Currently 929 end of therapy reports have been issued, 87% completed 6 or more therapy courses. Treatment and toxicity data are complete in 98%. TC-Top produced a markedly higher myelotoxicity resulting in treatment delays in 21% of the Topotecan courses. Grade 3/4 anemia occurred in 17% of all Topotecan courses, thrombocytopenia in 30%, neutropenia in 77%. There was no clinical relevance in terms of febrile neutropenia (2%) or infections (3%). The mean Topotecan dose/course for all 4 courses was 1.22 mg/m2. In non-hematologic toxicity no significant differences between TC and TC-Top could be observed. TC-Top is a safe first line regimen in advanced ovarian cancer. In both study arms TC and TC-Top the mean and median doses were given as scheduled, as were the median and mean intervals between therapy courses. Follow up will be updated in summer 2003. First efficacy data (response, progression free survival and survival) will also be available in summer 2003.

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Paclitaxel plus carboplatin versus paclitaxel plus alternating carboplatin and cisplatin for initial treatment of advanced ovarian cancer (AOC): long-term efficacy results

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Introduction: Carboplatin combined with paclitaxel are considered treatment of choice as initial chemotherapy for advanced ovarian cancer. We compared this combination with a regimen combining alternating carboplatin and cisplatin plus paclitaxel. The two platinum derivatives have been previously combined as they are considered not totally cross-resistant and as they share no overlapping toxicities, in order to increase the total platinum dose intensity and consequentially the disease outcome.

Material and methods: Patients with AOC after the initial cytoreductive surgery were stratified according to the FIGO stage and the presence of residual disease and were randomized to either combination of 6 courses of chemotherapy with paclitaxel at 175mg/m^2 as 3h infusion plus Carboplatin 7AUC (Arm A) or paclitaxel at the same dose plus Carboplatin 7AUC for cycles 1,3,5 and Cisplatin at 75mg/m^2 for cycles 2,4,6 (Arm B). Primary endpoints were disease free survival (DFS) and overall survival (OS).

Results: 247 patients are analyzed 121 in arm A, 126 in Arm B. 73% of the patients had stage III and 18% stage IV disease. Chemotherapy was generally well tolerated and treatment delays or dose reductions were not necessary. Toxicity and short-term efficacy results have been reported previously [Seminars in Oncology, 1997, 24 (5), (suppl 15), 15-21. Proc Am Soc Clin Oncol 1999;18:367a (1416)]. With a median follow up of 61 months statistically significant differences were not found, both in terms of time to progression (38 vs 39 months, p=0.95) and overall survival (40.6 vs 38.6 months, p=0.79). There is not also difference in 5-year survival rate (35% vs 39%) or 5-year disease free survival rate (23% vs 28%).

Conclusion: Both regimens are well tolerated and effective as first line chemotherapy of advanced ovarian cancer with very good long term outcome. Alternating cisplatin with carboplatin does not improve the results as compared with the standard carboplatin/paclitaxel combination.

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Influence of amifostine on neuroprotection in 1st-line treatment of advanced ovarian cancer with carboplatin/taxane-based chemotherapy - a double-blind, placebo-controlled, randomized phase II-study from the AGO Ovarian Cancer Study Group

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Neurotoxicity (NT) is one of the most important problem of platinum/taxane-based therapy of ovarian cancer (OC) with high impact on quality of life (QoL). We therefore performed a double-blind randomized and placebo-controlled multi-center trial to evaluate the influence of the cytoprotectant amifostine (AM) on NT in 1st-line therapy of OC with paclitaxel (T)/ carboplatin (C) +/- epirubicin (E). 71 patients were stratified for 1st-line chemotherapy with T 175 mg/m^2 and C AUC5 with or without E 60 mg/m^2 (q21x6) and randomized for premedication with AM 740 mg/m^2 i.v. (n = 37) or a placebo i.v. (n = 34) (30 min. prior to chemotherapy). NT was evaluated by an objective assessment with measurement of Patella (TRA) and Achilles tendon reflex activity, vibration perception threshold (VPT) and 2-point discrimination (2-PD) and additionally by a questionnaire concerning specific neurotoxic symptoms and motoric abilities. Supplementary, toxicities were assessed according to the NCI-CTC and QoL. The majority of NT criterions showed a significant impairment during therapy in both treatment arms. A significant protective effect of AM was observed for the objective assessment with TRA, 2-PD, and VPT with regard to intensity and time dependence of pathological findings. AM significantly improved a number of QoL-subscores, but failed to better the global health status score significantly (p= 0,3469). Toxicities according to NCI-CTC showed improved sensory neuropathy (0,0046) in the AM group but on the other hand a significant higher