MST was 30.3 weeks with 64% (CI = 51–81%) of patients surviving at 6 months (ST-6) and 28.6% (CI = 16–49%) at 12 months (ST-12).

Conclusion: TMZ as a second line regimen is a valid option in patients with heavily pretreated GBM.

1278 POSTER

Temozolamide (TMZ) in second-line treatment after pcv In glioblastoma multiforme (GBM). Experience from a single Portuguese Institution

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Purpose: Temozolamide is a new cytotoxic alkylant agent which has recently been aproved in Portugal for the treatment of recurrent high-grade glioma. A retrospective study was performed to assess the survival (Kaplan-Meier) of patients treated with TMZ at the time of relapse.

Methods: From September 1999 to March 2001, 16 patients with recurrent GBM who had prior PCV chemotherapy, were given TMZ 150-200mg/m2/day during 5 days every 28 day cycle.

Results: To date 16 patients with a medium age of 58 (ranges: 31-74) and a median KPS of 80% have been enrolled. The estimated one-year survival is 16%. The median overall survival was 6,5 months.

Conclusions: Despite the small scale of the sample, the overall survival achieved with TMZ is similar to other reports. These promising data suggest that randomized trials should be undertaken to assess its use in first-line therapy, its inclusion in combination chemotherapy regimes and its effectiveness with concurrent radiotherapy.

1279 POSTER

Phase I study with continuous infusion (CIV) dose escalated 5 day schedule topotecan (TPT) and radiation therapy (RT) for patients with previously untreated glioblastoma (GBM)

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Rationale: TPT has been shown to have (1) good penetration across the blood brain barrier in non-human primates (Sung Cancer Res 1994; 54: 5118), (2) significant anti-tumor activity against human brain tumor xenografts (Polina, J. Neurooncol 1998; 39:217) and (3) synergy with RT in humain glioma cell lines (J P Lamond J Neuroonco,1996; 30:1). The dose/schedule of topotecan chosen would be of value.

Objective: A phase I study was performed to determine the dose-limiting toxicity (DLT) and maximun tolerated dose (MTD) of CIV TPT in combination with RT in patients with GBM.

Methods: After surgery or stereotactic biopsy, patients received (1) RT using 2 Gy/fraction, 5 times/week with total dose of 60Gy reached in 6 weeks and (2) TPT with doses escalated from 0,6 to 1,0 mg/m2/d as CIV from day 1 to day 5 on week 1,3 and 5 during RT. DLT was defined as febrile neutropenia, grade 4 neutropenia more than 7 days, grade 4 thrombocytopenia, thrombocytopenia requiring platelets transfusion or any grade 3 toxicity except alopecia, nausea and vomiting. All patients had anticonvulsivant prophylaxis with valproic acid.

Results: 20 patients have been enrolled in the protocol between January and April 2001

DLT is hematologic with no other grade 3 or 4 treatment related toxicity except one confusion in one patient. MTD is 1,0 mg/m2/d and an intermediate level at 0,9 mg/m2/d is ongoing to determine the recommended dose. The table summarizes DLT according to TPT level and number of patients:

TPT Dose mg/m2	N	DLT	Type of toxicity
0,6	3	0/3	None
0,8	6	1/3	Thrombocytopenia gr 4 (1)
0,9	5	Ongoing	Not yet known
1,0	6	4/6	Thrombocytopenia gr 4 (3), platelet

Conclusion: The MTD of CIV TPT in association with RT in patients with GBM is 1,0 mg/m2/d, The DLT is hematologic. 0,9 mg/m2/d appears to be the appropriate phase II dose, but needs to be confirmed.

1280 POSTER

A phase II study evaluating the efficacy and safety of temozolamide (tmz) post and concurrently with radiotherapy (RT) in the treatment of patients with previously untreated high grade gliomas

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Purpose: It is known that the prognosis of patients with high grade gliomas is dismal. It is slightly improved by the use of RT. The addition of TMZ, as a new chemotherapeutic agent in the treatment of these patients, is studied.

Methods: Since November 1997, we have studied 31 patients suffered from high grade gliomas.Eligible histologies include glioblastoma multiforme (28 patients) and anaplastic astrocytoma (3 patients). All patients received RT at a total dose of 60-64 Gy, 2 Gy per fraction, within 6-6.5 weeks and they hadn't received prior chemotherapy. In group I (14 patients) TMZ was prescribed 3 weeks after the completion of RT at a dose of 200 mg/m2/day for 5 consecutive days. In group II (17 patients) TMZ was administered concurrently with RT at a dose of 150 mg/m2/day for 5 concecutive days. At the end of RT patients received 2 cycles of TMZ. We continued with TMZ at a dose of 200 mg/m2/day, every 28 days. The dimensions of the lesions were evaluated 3 times during the study with MRI, at the beginning of RT, after 3 and 6 cycles of TMZ.

Results: In group I, patients had a median age of 54 years (ranged from 27 to 73 years) and in group II, patients had a median age of 58 years (from 26 to 83 years). At the time of enrollment in the study, all patients had Karnofsky Performance Status (KPS) greater than or equal to 70. In group I 10 patients and in group II 7 patients had undergone surgery before RT, the rest had undergone stereotactic biopsy. Adverse events were nausea and vomiting (55%), fatigue (40%), constipation (45%). Hematological undesirable consequenses included leukopenia (4/14, 5/17), thrombocytopenia (7/14, 11/17), anemia (2/14, 3/17). Many patients had high prices of serum liver enzymes (AST, -GT). Two patients (1/14, 1/17) discontinued treatment because of adverse events related to TMZ. During the study, 16 patients (8/14, 8/17) were died after a mean survival of 11 months in group I, and of 9 months in group II. Fifteen patients (6/14, 9/17) are still alive with a mean survival of 18 months in group I, and of 7 months in group II. In group I, the mean PFS was 12.5 months and in group II 7 months.

Conclusions: According to our study, it seems evidently that the administration of TMZ at a dose of 200 mg/m2/day after the completion of RT is more effective in terms of PFS and overall survival. The KPS of the patients was satisfactory during the study and TMZ showed a good toxicity profile and desirable antitumour activity.

1281 POSTER

Gemistocytic astrocytoma – Astrocytoma II with unfovorable prognosis

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Three major histopatological variants of diffusely infiltrating astrocytomas are recognised: fibrillary (FA), protoplasmatic (PA) and gemistocytic. They are designed in WHO classification of tumours as grade II. Gemistocytic Astrocytoma (GA), the second most common variant account for no more 20% of astrocytoma. GA often behave more aggressively than other types of diffusely infiltrating Astrocytomas, and around 80% of these tumours progress to GBM. Surprisingly, the vast majority of gemistocytes are in a nonproliferative state, which suggest terminal differentiation. However GA contain highly variable small glial cell component which appears be mitotically active. P53 mutations are a genetic hallmark of GA, whereas the incidence of p53 mutations in astrocytomas of other variants is low.

Material: In the years 1983 - 98 in our Hospital there were treated 462 adults with Astrocytomas I–IV. In 34 pts were diagnosed GA in 20 and Anaplastic GA in 14. There were 25 men and 9 women; the median age was 44.9. Tumours in the temporal lobe were most often. All pts were undergone surgery procedure following by radiotherapy (60 Gy for the tumour bed). Chemotherapy (PCV) was done for 13 pts with the tumour test after operation.

Results: Material was analysed according to following tests Cox, Cox-Mantel, log-rank, Wilcoxon Peto Peto. The median recurrence time free was 14 m. 25% of pts died in the 37 m after operation, 50% pts survived 77 m, and 25% live out more than 95 m.

Conclusions: The small group of pts renders presentation of univocal conclusions impossible. The treatment of pts with AG gives worse results than in the cases of AF and AP. Cht did not better results.

1282 POSTER

Whole brain irradiation versus limited fields in the treatment of high-grade malignant gliomas

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Purpose: Delineation of the target volume is a controversial issue in radiation treatment of high grade malignant gliomas. Our purpose was to verify if the choice of different volumes in radiation treatment influence the overall survival (OS). The effect of age, performance status, extent of surgery and histology was analysed for prognostic importance.

Methods: From January 1995 to June 2000, 75 patients (pts) with histologically confirmed malignant astrocitomas were treated. No patient was lost for follow-up. The total dose of 50-60 Gy was applied with 6Mv or Co60 teletherapy device, in one day fraccion of 1.8-2 Gy. The entire brain was irradiated in 40 pts (52%). In 11 pts (19%), the entire brain was first irradiated, and in a second phase the total doses were achived with reduced fields. Twenty four pts (29%) were treated with reduced fields directed to the treatment volume encompassing the contrast-enhancing lesion with a 2 cm margin based on preoperative MRI and CT. Survival was calculated using the Kaplan-Meier method. Significance of the differences was analysed with Log Rank test. The significance level was $p < 0,05$.

Results: Median survival was 9 months (range 2-68 months). There were 45 males (60%) and 30 females (40%), with a median age of 62 years (range 23-77 years). The pts were classified in three groups of age: <45, 45-65 and > 65 years. The OS for these groups were 21, 9 and 8 months (p= 0,0003). The median WHO performance status score was 2. Twelve pts had a score 0 (16%), 31 a score 1 (41%), 20 a score 2 (27%), 7 a score 3 (9%) and 5 a score 4 (7%). The OS for these groups were 25, 11, 6, 7 and 6 months (p=0,0003). Histology consisted of anaplastic astrocytoma (AA) in 12 (16%) and glioblastoma multiforme (GBM) in 63 (84%). The OS for AA was 15 months and for GBM 9 months (p=0,03). Eighteen (24%) pts underwent biopsy, 21 (48%) gross total resection, and 36 (48%) subtotal resection. The OS for these groups were 9, 10 and 9 months (p=0,28). The OS for pts who irradiated the entire brain was 7 months, while for those that irradiated the entire brain plus a boost was 11 months. The OS for pts who were treated with limited fields was 16 months (p= 0,0006).

Conclusion: In our series, age, performance status and histological subtype proved to be important prognostic factors. In high-grade gliomas there is no benefit in the irradiation of the entire brain. The best results are for pts who were treated with limited fields of irradiation.

1283 POSTER

Concomitant radiation therapy and temozolomide (TMZ) in the treatment of multiform glioblastoma and anaplastic astrocytoma: a pilot study

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TMZ has demonstrated efficacy against recurrent malignant gliomas (MG). We evaluated the tolerance of TMZ associated with radiation therapy (RT) in post surgery treatment of incompletely resected MG. From September 1998 to Dicember 2000, we treated 18 patients (15 glioblastomas, 3 anaplastic astrocytomas) with incomplete resection after surgery and an average residual disease of 3.25 cm (range 2-5 cm). Mean age was 58.6 (range 37-73 years); 7 patients were > 65 years. TMZ was given with a weekly schedule (150 mg/m2 daily for 5 days, repeated every 28 days for three times). TMZ was administered at the beginning of the fourth week of RT (dose 30 Gy) in 7 patients (Group A) and at the first day of RT in 11 patients (Group B). The average total dose was 65.6 Gy (range 54-70) with standard schedule. 3-D planning was performed for all patients with customized shielding and multiple coplanar beams arranged to include Planning Target Volume within the 95% isodose line. Two patients in group A completed RT but not the planned dose of TMZ: 1 due to progression after one cycle of TMZ and 1 due to kidney failure after two cycles. Two patients in Group B developed grade IV leuko-thrombocytopenia after two cycles of TMZ (RT 54 and 60 Gy). Of the latter, one died and one finished planned RT with some delay, obtaining partial remission. All 4 patients were older than 65 years. In the other patients, no toxicity was observed. Out the 16 patients that completed treatment an MRI/CT showed: 4 progressions, 5 stable diseases, 5 partial responses and 2 complete response (1 multiform glioblasoma and 1 anaplastic astrocytoma). To date, 9/18 patients are alive with a mean follow up of 16 months (range 8-21) from surgery. A overall survival analysis with Kaplan-Meier method showed a 35% at 24 months.

Conclusion: Concomitant RT and TMZ is feasible and well tolerated (compliance 70%) in MG patients with incomplete surgical resection. We had a tolerance problem in the patients older than 65 years.

1284 POSTER

Simultaneous radio-chemotherapy of malignant gliomas with topotecan

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Purpose: Because of the pronounced radioresistance of glioblastoma multiforme (GBM) the prognosis of this disease remains poor. Therefore, we investigated the impact of an additional simultaneous chemotherapy with the topoisomerase-I-inhibitor topotecan (TTC) on the quality of life and toxicity of radiotherapy.

Materials & Methods: In this multicenter trial patients with histologically proven GBM underwent a simultaneous radio-chemotherapy. Including pilot phase 60 patients, 41 male and 19 female, were treated. Age ranged from 26 to 76 years, the mean was 57 yrs. Conventionally fractionated conformal radiotherapy was performed with daily doses of 2.0 Gy to a total dose of 60 Gy. One hour prior to irradiation 0.5 mg (absolute dose) of TTC were administered intravenously resulting in a cumulative dose of 15 mg. Hematologic and non-hematologic toxicity and survival time were recorded. Quality of life was assessed by Karnofsky performance scale (KPS) and Spitzer-index (SI).

Results: Median administered dose of radiation was 60 Gy (32.4-76 Gy). Median cumulative TTC dose was 15 mg (5-19 mg). Grade-III toxicity was found in 6 cases (2x hematologic, 2x motoric disorder, 1x infection, 1x nausea) and grade-IV toxicity in 3 cases (1x esophagitis, 1x motoric disorder, 1x mental disorder). Two patients died of septic disease most likely caused by steroid induced immunosuppression. Mean KPS and SI initially, at the end of therapy and 6 wks after therapy showed values of 87%, 81% and 80% and 19 pts, 18 pts and 19 pts, respectively. The differences were all not significant. Median survival time was 13.5 months. This was slightly longer than a historical collective with a median survival of 10 months.

Conclusion: This multimodal approach for patients with GBM is well tolerated. Quality of life remains preserved and outpatient treatment is possible.

1285 POSTER

A phase II trial of topotecan and radiation therapy for CNS-metastases of patients with solid tumors

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Once the diagnosis of CNS-metastases in patients with solid tumors is etasblished, the prognosis is poor and there is a need for new concepts in therapy.

This is an interim-analysis of 68 patients with CNS-metastases due to solid tumors (14 SCLC, 36 NSCLC, 6 breast, 2 unknown) treated with a simultaneous therapy of topotecan and whole brain radiation (20 x 2 Gy, 20 x 0.4 mg/m* topotecan as short infusion within 2 h to radiation therapy) in a phase II clinical trial. At this time 54 patients finished the therapy, 14 patients are still in course, 45 patients are evaluable for toxicities and survival, 36 patients are available for evaluation of remission. Hematologic toxicity: anemia grade 3 one, grade 4 one; neutropenia grade 3 two, grade 4 one; thrombopenia grade 3 three, grade 4 two. Non-hematologic toxicity: sensorium grade 3 five; stomatitis grade 3 two; infection grade 3 one, grade 4 four. Infection occurred only in the beginning of the study if dexamethason was given at dosages > 12 mg daily. Remission: out of 36 at this time