diameter on axial plane images. Crude LC rate was 81% (25/31). Six patients failed locally, 2-3 months after FSRT(median 9). Actuarial 1-year LC rate was 74%. Median survival time was 351 days, with actuarial overall survival rate at 12 and 18 months of 48% and 14% respectively. Thirty-eight percent of patients (11/29) developed new metastases outside the treatment volume after 2-24 months (median 11)and 4 received whole-brain irradiation as salvage treatment. In the majority of patients (10/29) the cause of death was systemic tumor progression. All treatments were well tolerated and no acute complications were seen, with the exception of transient headache and limited nausea.

**Conclusion:** This retrospective study suggests that FSRT with few fractions and a short treatment period is a tolerable and effective form of intensive local treatment of brain metastases.

1274 POSTER

## Three different fractionation schemes in glioblastoma multiforme: a single center experience with 430 patients

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**Purpose:** To evaluate the role of fractionation in the management of newly diagnosed glioblastoma multiforme (GBM).

**Patients and methods:** From January 1980 to June 2000, 430 consecutive patients with histologically confirmed GBM were treated at our institution. Median age was 59 years (19-81), Karnofsky Performance Status >/= 70 in 290 patients. 86 patients had a biopsy, 344 underwent resection. Primary radiotherapy was given in conventional fractionation - 5 x 2.0 Gy, total dose 60.0 Gy (n = 97). Postoperative radiotherapy was given hypofractionated - 5 x 3.5 Gy, total dose 42.0 Gy - (January 1980 - July 1983; n = 104) or hyperfractionated - 5 x 3 x 1.5 Gy, total dose 54.0 Gy (August 1983 - June 2000; n = 229). Survival probabilities were computed using the method of Kaplan-Meier.

**Results:** Median actuarial survival probabilities were as follows: All patients 8.6 months; biopsy 5.9 months vs. resection 9.0 months (p = 0.03); hypofractionation 8.2 months vs. hyperfractionation 9.05 months vs. conventional fractionation 8.5 months (p = 0.56). In a proportional hazards model, independent variables indicating a better prognosis were younger age (< 59 years vs. >/= 59 years: RR 0.84, 95%-CI 0.76-0.93), good performance status (KPS >/= 70 vs. KPS < 70: RR 0.83, 95%-CI 0.75-0.92), normal LDH level (LDH < 240 vs. LDH >/= 240: RR 0.77, 95%-CI 0.67-0.89) and total dose (RR 0.98/extra Gy, 95%-CI 0.97-0.99).

**Conclusions:** In this pure GBM series fractionation did not affect survival. Shortening treatment time by modifying fractionation does not compromise life expectancy. Besides the validation of known prognostic factors like age, KPS and total dose we found elevated LDH levels to have a strong negative influence on survival.

1275 POSTER

## Temozolamide in previously treated high-grade gliomas patients

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**Objectives:** To assess the efficacy and toxicity of temozolamide in high grade glioma patients previously treated.

**Patients and Methods:** Histologically proven high grade glioma patients (pts) with measurable disease were included. Temozolamide was administered at a dose of 150 mg/sqm five consecutive days every four weeks. If no grade III or IV toxicity appeared dose could be increases up to 200 mg/sqm. Response was assessed every 3 courses according to McDonald's criteria and therapy maintained until progression or unacceptable toxicity.

**Results:** 49 patients have been included, 33 (67%) males, median age 48 (22-69), ECOG performance status 0/1/2 in 5/23/21 pts. Median tumour area was 13.5 cm2 (1-63) Previous chemotherapy lines 0/1/2/3 in 4/36/5/3 pts, with a median of 4 chemotherapy courses per patient (0-8). All except 1 had received radiotherapy. Histology was glioblastoma 30, anaplastic astrocytoma 14, oligodendroglioma 2, and oligoastrocytoma 3.

**Overall response rate was 22:**4%, with complete response (CR) in 4 patients (8.2%, 2 patients with oligoastrocytoma and 2 with anaplastic astrocytoma), and partial response (PR) in 14.3% (7 pts). stable disease (SD) was achieved in 22.4%. Response according to histology was glioblastoma 10% PR (3), 33% SD (10), overall response 10% anaplastic astrocytoma 14.3% CR (2), 21.4% PR (3), 64.3% progressive disease (PD) (9), overall response 60% and oligodendroglioma or oligoastrocytoma 40% CR (2), 20% PR (1), 20% SD and 20% PD, overall response (60%). Actuarial median survival of all patients was 36 weeks (CI95% 27-44). glioblastoma 29 weeks (CI95% 12-45), anaplastic astrocytoma 46 weeks (CI95% 3.5-88), median survival is not reached for oligodendroglial tumours with a median follow up of 88 weeks (21-197).

No grade III or IV toxicity has been reported, and main toxicity were mild thrombocytopenia and moderate nausea easily controlled with 5-HT3 antagonists.

**Conclusions:** Temozolamide is active in high-grade glioma patients, even if previously chemotherapy treated. Anaplastic astrocytoma and oligodendroglial tumours appear to have better response and survival. This treatment is well tolerated with minimal toxicity

1276 POSTER

## Expression of PDGF-R, DCC, MDM2 and P16 in human gliomas

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Gliomas constitute a group of very aggressive and almost incurable primary brain tumors. Changes in the expression of the oncogenes PDGF-R and MDM2 and that of the suppressors DCC and p16, have been associated to tumor progression. In this work we studied, by immunohistochemistry, the expression of the aforementioned molecules in 41 gliomas of different histological grade of malignancy [low grade (LGA), anaplastic astrocytoma (AA) and glioblastoma multiform (GBM)]. A high expression of PDGF-R (>50% of positive cells) was found associated with the histological grade (40% of GBM vs. 15% LGA and AA tumors, NS). Only a few cases presented overexpression of the oncogene MDM2, with no differences among the three groups of gliomas, and the expression of DCC was lost in only 11% of the GBM. On the other hand, found a significant association between the loss of expression of the suppressor p16 and the histological grade (LGA: 0%, AA: 12% and GB 26%, p<0.05). This correlation was not modified when variables such as sex, age and Karnofsky status were introduced in the analysis. Among all the molecules analyzed, only p16 staining showed a significant correlation with overall survival. While 78% of the patients with the longest survival (>1 year) expressed p16, only 22% of those who were alive for less than one year after diagnosis did (p<0.05). In conclusion, the association between the loss of the cell cycle inhibitor p16 expresssion in human gliomas and the histological grade was independent of the other prognostic variables studied. Moreover, this lack of expression showed a correlation with a shorter overall survival.

1277 POSTER

## Temozolomide as a second line regimen after BCNU and procarbazine in recurrent glioblastoma multiforme: A phase II study

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**Purpose:** To investigate the efficacy of temozolomide (TMZ) in relation to response rate, toxicity, and progression free survival at six months (PFS-6), a phase II study was conducted in patients with recurrent glioblastoma multiforme (GBM) following surgery plus radiotherapy and a first-line regimen based on nitrosourea, procarbazine and vincristine.

**Patients and Methods:** 42 patients with GBM, of which 8 (19%) were previously low grade astrocytoma or oligodendroglioma, were administered TMZ at the dose of 150 mg/m$^2$/daily for five days every 4 weeks.

**Results:** The response was assessed in all 42 patients: we observed 2 complete responses (CR) (4.7%), 6 partial responses (PR) (14.3%), and 9 stable disease (SD) (21.4%), with CR + PR = 19% (95% Confidence Interval [CI] = 7–31%). The median TTP for all 42 patients was 11.7 weeks, (CI = 9–22%) while progression free survival at 6 months (PFS-6) and at 12 months (PFS-12) was 24% (CI = 14–42%) and 8% (CI = 2–27), respectively.

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.