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Malignant gliomas in elderly: short course radiotherapy is feasible and effective

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The benefit of standard treatment of malignant gliomas in older patients is still debated. In order to assess the effect of short course schedule of radiotherapy 21 consecutive patients older than 70 years (range 70-78) with malignant supratentorial gliomas were studied. Patients underwent surgery followed by a course of radiation therapy: total dose of 45 Gy were administered in 2 cycles (split 15 days), 2.5 Gy /fraction, 3 fractions daily for 3 days/cycle with limited fields (ICRU 50). 5 patients had also nitrosurea based chemotherapy (max 4 cycles). The mean KPS before starting radiotherapy was 70. The overall median survival was 9 months, the median time to progression was 6 months. 25% of patients survived over 18 months. The only significant prognostic factor was extention of surgery. There was no case of radiotherapy induced dementia with this regime. This study suggests that some patients older than 70 years with good KPS may benefit from the treatment with surgery followed short course of radiotherapy.

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VM-26 and Carboplatin in patients with oligodendroglioma recurrent after PCV and temozolomide chemotherapy

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Background: Oligodendroglioma is a chemosensitive tumor. In published series, standard PCV obtained a response rate (RR) of 60-70% with a Time To Progression (TTP) of 12-18 months for responders, and second line chemotherapy with temozolomide achieved a RR of 43-63% and a TTP of 6.7 months. At progression, no cross-resistant chemotherapy options are available, although further treatments might be indicated for patients maintaining an acceptable neurologic function.

Objectives: To determine RR, TTP, and toxicity of the association of carboplatin and VM-26 in adult patients (pts) with oligodendroglioma (OD) or mixed oligoastrocytoma (OA) progressive or refractory to radiotherapy, PCV and temozolomide chemotherapy.

Methods: 23 eligible pts with median age 47 years (range 28 -64.4) and median KPS 80 (range 40-90) were enrolled and received carboplatin (350 mg/m^2 on day 1) and VM-26 (50 mg/m^2 on days 1 to 3), every 28 days. All pts had measurable contrast-enhancing disease at MRI, and 17 of them were pure OD at the most recent pathological diagnosis.

Results: There were 2 PR (8.7%), and 12 stabilizations of disease (52%). Median TTP was 4.5 months, and PFS at 6 months was 34.2% (CI 95%= 19-61%), with 50% (CI 95%= 32-79%) of pts alive at 12 months after the start of therapy. Pure OD phenotype was prognostic both for response (p=0.02) and survival (p=0.005).

Toxicity: A total of 103 cycles were delivered (on average 4.4 cycles per pt, range 1-9). Myelosuppression was moderate, with G3 neutropenia and G3 thrombocytopenia in 2 (8.7%) and 2 (8.7%) pts, respectively. One pt had a deep vein thrombosis, one a gluteal abscess concomitant with G3 neutropenia. Three pts (13%) required dose reduction to 75%, while 18 cycles (17.4%) were delayed for 1 or 2 weeks due to hematological toxicity.

Conclusion: Carboplatin and VM-26 achieved a moderate RR, but appear to delay progression in patients with heavily pretreated oligodendroglial tumors, with manageable toxicity.

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The role of radiosurgery/stereotactic external beam radiotherapy with a linear accelerator in treatment of brainstem gliomas

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Objectives: Brain stem gliomas are among the most resistant brain tumors to therapy. Because of the critical location of these tumors in an area of the brain where many important neurogenic structures are closely confined, surgical resection is usually impossible except in the more exophytic type of tumor which is much less common than the intrinsical tumor of the brainstem. Stereotactic radiosurgery/external beam irradiation allows a substantial increase in total dose at the tumor site while sparing most of the normal brain tissue. The aim of this study was to evaluate the efficacy and safety of radiosurgery/stereotactic external beam irradiation (SRS/SEBI) in patients with brain stem gliomas.

Methods And Materials: From June 1996 to December 2002, 31 patients with brain stem gliomas, 19 male and 12 female, were treated with SRS/SEBI. The median age at presentation was 39.5 years (range 6-67 years). Duration of symptoms before diagnosis varied from 20 days to 5 years, with a median of 112 days. 7 patients had biopsy proof of glioma, the rest were diagnosed on the basis of computer tomography (CT) and/or magnetic resonance (MR) scans. Most of the tumors (64%) arose in the pons. Tumor types were categorized as focal in 10 patients, and diffuse in 21 patients. 6 patients were treated with SRS Stereotactic radiosurgery, a technique delivering a relatively large single dose to an intracranial target with great accuracy and the others were treated with SEBI stereotactic external beam irradiation, similarly accurate radiation as SRS given over multiple treatments.

Results: Of the total 31 patients, complete remission (CR) was observed in 7 patients, partial remission (PR) in 12 patients, stable disease (SD) in 7 patients, and progressive disease (PD) in 5 patients post SRS/SEBI. The mean overall survival, progression free survival, and disease free survival from the first date of SRS/SEBI were 14.6 months, 12.7 months, and 5.5 months, respectively. On univariate analysis, focal disease and tumor response of CR after SRS/SEBI favor survivals significantly. The pattern of failure was exclusively local. Treatment morbidity included dizziness in 7 patients, mild headache in 5 patients, mild nausea and vomiting in 3 patient, and late symptomatic edema in 4 patients. All of these effects were medically manageable.

Conclusions: Because of our encouraging local tumor control and acceptable toxicity, SRS/SEBI may represent an alternative choice of treatment for patients with newly diagnosed or recurrent brain stem gliomas especially for focal disease.

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Iodine-125 anti-EGFR radioimmunotherapy of malignant gliomas: search for optimal criteria of eligibility

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Radioimmunotherapy with antibodies against epidermal growth factor receptor (EGFR), labeled with ^{125}I, has been proposed for completion of radical treatment in multiform glioblastomas and anaplastic astrocytomas (Brady *et al.* 1995) and has been reported to prolong total survival. The underlying mechanisms encompassed the binding of anti-EGFR monoclonal antibody 425 to membrane EGFR, the internalization of the complex and its translocation to the cell nucleus and the genotoxic effect of Auger electrons emitted by radioiodine-125.

In the study we address the question whether anti-EGFR-^{125}I radioimmunotherapy influences the disease-free survival in patients with malignant gliomas treated by previous radical surgery and concomitant teleradiotherapy.

Eighteen patients with primary glioblastomas or anaplastic astrocytomas were previously treated by macroscopically radical surgical resection of tumor confirmed by NMR ^{1}H spectroscopy and then randomized to radiotherapy+radioimmunotherapy arm (8 patients) or radiotherapy alone (10 patients). All patients were irradiated with 60 Gy with three-dimensional conformal non-coplanar technique. Radioimmunotherapy with 50 mCi of ^{125}I-labelled anti-EGFR monoclonal antibody 425, kindly provided by prof. L. Brady, was started during the fourth week of radiotherapy and was repeated three times in one week intervals.

Time of follow-up was 4-18 months with median time of 10 months in the radioimmunotherapy arm and 9 months in the control arm. Recurrence was diagnosed in all patients treated by ^{125}I anti-EGFR and in 6 patients in the control arm. Median time to recurrence was 2 and 4 months, respectively. No statistically significant differences in the time to recurrence and in actuarial total survival were observed between both groups of patients.

We consider the obtained results as unsatisfactory, thus we intended to improve the eligibility criteria by analyzing EGFR expression in the resected tumors. Immunohistochemical (wild type of receptor) and real-time PCR

analysis (wild and mutated receptors) was performed in a separate group of 40 malignant gliomas obtained after surgery in order to evaluate the frequency of EGFR overexpression.

In conclusion, we propose to select patients for further studies of ^{125}I-anti EGFR therapy in malignant gliomas by investigation of wild and mutated EGFR expression in the resected tumor tissue.