8740 POSTER

Radiosurgery of Brain Metastases Using Leksell Gamma Knife − Results of 400 Treated Patients

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Background: To analyze treatment results,complications and prognostic factors for survival.
Material and Methods: During a period of 8 years 400 patients (pts) with brain metastases underwent stereotactic irradiation using Leksell gamma knife (242 with solitary and 158 pts with multiple lesions) in a single session. Median of planning target volume (PTV) was 6,800 mm^3, median of minimum dose to the PTV was 18 Gy (16−24). The dosage was prescribed with respect to the following conditions: previous irradiation and location of lesion in the brain. The severity of symptoms (neurological functional class NFC) and radiation toxicity were evaluated using RTOG/EORTC system and performance status by Karnofsky rate (KF). In the group of patients we analyzed variables affecting PFS after treatment and radiation related toxicity (number of lesions, histology, age, location, time to brain metastases occurrence, NFC and KF before treatment). We used univariate (Kaplan–Meier with Log-rank test) and multivariate analysis (Cox regression) to detect differences in survival curves.
Results: Complete and partial regressions were noticed in 74%, progression in7%, local recurrence in 10%. The median PFS for solitary lesions was 10 months, for multiple 7 months. The best results were observed in pts with metastases of renal cancer − median of PFS was 12 months. Among mentioned variables we detected as significant positive prognostic factors: solitary lesions, histology-renal cancer, asymptomatic lesions or NFC 1, 2, KF higher than 70%, the minimum applied dose 20 Gy, the interval to occurrence of brain metastases longer than 19 months. In our group of pts we observed acute toxicity grade 3,4 in 20% of pts and late in 5% of cases. PFS longer than 5 years was noticed in 9% of treated patients with median 90 months (60–144).
Conclusion: Radiosurgery represents an effective treatment modality for brain metastases (response rate 74%) with acceptable incidence of late complications (5%).

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Radical Surgery After Chemotherapy as a New Strategy in High Grade Glioma

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Background: While the impact of extent of surgical resection on the survival of GBM is questionable, the neurosurgeons still attempt to remove as much as possible from the tumour. However, complete resection is often impossible due to highly infiltrative nature of these tumours.
Material and Methods: We report a cohort of 5 patients with supratentorial malignant glioma. Because of the infiltrative nature of the tumour, if surgery was chosen the tumour could be resected only partially. We decided to try chemotherapy instead in an attempt to reduce the tumour before surgery.
Results: The patients were treated with two monthly standard cycles of temozolomide (150–200 mg/kg/day for 5 consecutive days) and two biweekly cycles of bevacizumab at 5 mg/kg. The decrease of tumour size and peritumoral edema rendered the tumour amenable to radical surgery which was performed subsequently without sequelae. Currently, the patient are completing their radiotherapy concomitantly with temozolomide.
Conclusion: Based on the success of these cases, we are suggesting a new therapeutic strategy for GBM that cover large and eloquent areas preventing their complete resection. The strategy we propose enhances the chances for radical surgery in the management of these tumours. Will this strategy also prevent the local recurrences if we perform a removal at 2 cm margin from tumour burden?! Further exploration is needed.

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Temozolomide and Lapatinib Combination in Patients With Recurrent High Grade Gliomas − a Phase I Study of the Hellenic Cooperative Oncology Group (HeCOG)

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Background: No effective salvage treatment exists for recurrent high grade gliomas. However EGFR amplification/overexpression and EGFR vIII mutation are common events in gliomas. Therefore, EGFR tyrosine kinase inhibitors (TKI) are potential options for targeted therapy in these tumours. We undertook this phase I study to investigate the feasibility and safety of the combination of an alkylating agent temozolomide (TMZ) and a dual TKI of EGFR and ErbB2, lapatinib (LP), and define the maximum tolerated dose (MTD) in patients with relapsed high grade gliomas.
Materials and Methods: Patients with recurred high grade gliomas and ECOG PS 0−2, who had been previously treated with either adjuvant or first line treatment with radiotherapy and TMZ, were enrolled in this dose escalation study of LP. TMZ was administered at a fixed dose of 200 mg/m^2 d1-d5 every 28 days. Starting dose of LP was set at 1000 mg daily continuously, escalated by 250 mg in cohorts of minimum three patients (3+3 design).
Results: Between 1/2009 and 10/2010 16 patients (9 Males/7 Females) with a median age of 60 years entered the study. Fourteen patients had a glioblastoma multiforme histology and two patients had anaplastic astrocytoma. Three dose levels (DL) of LP were investigated: 1000 mg od (11 patients), 1250 mg od (4 patients) and 1500 mg od (1 patient, protocol violation). A total of 55 treatment cycles have been delivered (median 2.5, range 1−10). Two patients are still on treatment for more than 7 cycles. DLT hematological toxicity was observed in 2 patients at the second DL of LP at 1250 mg od (neutropenia grade 4/anemia grade 3 and thrombocytopenia grade 4). MTD was defined at first DL of lapatinib 1000 mg od. Hematological toxicity was the most common adverse event (69%, any grade). Non-DLT grade III/IV hematological toxicity was observed in 2 patients at the expanded first cohort. One radiological partial response was seen and 4 patients had stable disease. Median PFS was 2.4 months and median survival was 5.9 months.
Conclusions: Combination of TMZ and LP is feasible and safe with manageable toxicity. The activity of this combination in patients with recurrent high grade gliomas should be investigated in phase II trials. Molecular analysis of predictive factors is underway.
The phase I part of the trial (ANZCTR Req. No 00336822) has completed. The trial is sponsored by HeCOG.

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Efficacy of Fotemustine in Recurrent Malignant Glioma According to Time to Adjuvant Temozolomide Failure − a Pooled Analysis

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Recurrent glioblastoma (GBM) patients have few therapeutic options and the use of nitrosoureas, alternative schedule of TMZ and new target therapy have been widely studied. Recently Perry and colleagues (JCO 2010) have demonstrated that time to adjuvant temozolomide failure seems to be predictable to dose-intense TMZ treatment clinical response.
The aim of our pooled analysis was to assess the efficacy of fotemustine in recurrent GBM patients according to time to adjuvant TMZ progression.
Methods: Patients with GBM who failed the standard Stupp regimen have been treated with a nitrosoureas based regimen of fotemustine (FTM) 75–100 mg/sqm at day 1, 8, 15 (induction phase) and after 4/5 weeks of rest 100 mg/sqm every 21 days. The primary endpoint of the study was 6-months progression free survival (PFS-6m), Overall survival at 1 year (OS1 y), response rate (RR) and toxicity were secondary endpoints. Patients were stratified in 3 groups according to time to TMZ failure: GBM patients failing during the first 6 months of adjuvant TMZ (B1), those who failed after more than 6 months of therapy (B2) and GBM patients who recurred after a treatment-free interval (B3).
Results: Six Italian centers participated in this study. At that time preliminary results are available: 119 patients with recurrent GBM have been evaluated. Results have been summarized in the table.

	B1 (%)			B2 (%)			B3 (%)		
	PSF-6m	OS1 y	RR	PSF-6m	OS1 y	RR	PSF-6m	OS1 y	RR
FTM	24.5	24.5	12.2	31.3	31.3	18.8	34.2	28.9	7.9
TMZ[1]	27.3	27.3	3	7.4	14.8	0	35.7	28.6	11.1

[1]Perry et al JCO 28:2051- 2057, 2010.

Conclusion: Fotemustine is a valuable therapeutic option for patients with recurrent GBM, not depending on time to adjuvant temozolomide failure and also patients recurred after 6 cycles of adjuvant TMZ (B2) seem to get a benefit from FTM treatment. A prospective randomized trial is warranted to define if TMZ and FTM have a different pattern of response in recurrent GBM.