1270 POSTER

Local fluorouracil releasing microspheres (FU-M) with early radiotherapy (RT) in high grade gliomas (HGG): Preliminary safety assessment of a randomized phase II trial of early RT with or without FU-M in patients with complete surgical resection of HGG

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Rationale: HGG and especially glioblastoma multiforme have a poor prognosis. Median survival of patients (pts) treated with surgery and RT is 36 weeks (w), 40–50 w with the addition of chemotherapy. Biodegradable microspheres (M) are made of (d, l-lactic acid-co-glycolic acid) and are metabolized into CO_2 and H_2O. FU is a radiosensitizing and minimally neurotoxic drug, which is slowly released from M locally. Studies in rats with orthotopic tumoral implantation have shown FU-M and RT combination to be more effective than either treatment alone. Pilot clinical experience (Cancer 1999; 86: 325–30) motivated further development. Objectives of the ongoing multicentric randomized phase II trial (60 evaluable pts planned) are to assess efficacy (local progression free survival), safety and overall survival.

Methods: Pts with clinical and radiological suspicion of HGG with expected complete resection of tumor were randomized before surgery to local FU-M plus early RT (A) or early RT alone (B). Pts were treated after confirmation of the diagnosis by frozen biopsy during surgery. FU-M were injected around the walls of the resection cavity (A) and RT was begun within 7 days in both arms (59.4 Gy in 6.5 w). Pts in both arms received steroids during RT. Pts were assessed by MRI at baseline and every 3 months and by CT scan 24 hours and 6 w post surgery.

Results: 27 pts included from July 99 to December 00 in 8 centers are evaluable for safety, 13 A and 14 B. Glioblastoma/oligodendroglioma 10/3 in A and 13/1 in B, median age 53 years (35–69) in A and 54.5 (29–67) in B. Sex (m/f) 9/4 in A and 7/7 in B. Median dose FU-M received: 127 mg (106–132). Median volume FU-M received: 2.4 cm^3 (2–2.5). Median dose RT received: 59.4 Gy (59.4–60) A and 59.4 Gy (52.2–60) B. There was no definitive RT discontinuation due to toxicity. RT interruptions: 3 pts A (5 days, 7 days, 3 w) and 3 pts B (3 days, 7 days, 4 w). Alopecia 3 A, 5 B. No local healing complications were observed. Neurological adverse events occurred in: 9 pts A and 5 pts B, most of them reversible. 1 pt B died during treatment due to pulmonary embolism (after 52.2 Gy).

1271 POSTER

Brain metastases treated by Leksell gamma knife – Results and prognostic factors for patients

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Purpose: To analyze treatment results, complications, prognostic factors and their significance in patients treated with Leksell gamma knife (LGK) for brain metastases (BM).

Methods: During 6 years 400 patients (pts) with brain metastases were treated by gamma knife with minimal follow up 10 months. There were 242 (61%) patients with solitary brain metastasis (SBM) and 158 (39%) with multiple (2–4) lesions (MBM). Median patients age was 58 years (ranged 33 to 76 years), the median treated volume was 7.5 ccm (ranged 0.4 to 35.5), the median of dose to margin was 21.5 (range 16 to 30 Gy) and median neurological functional class was 2.6 (range 1 to 3). The histological subtypes were as follows: 140 patients (35%) non-small lung cancer, 70 (17.5%) renal cell carcinoma, 52 (13%) breast carcinoma, 49 (12.3%) melanoma 39 (9.7%) colorectal carcinomas, other types in 13 (3.3%) and 37 (9.2%) with unknown primary location of malignant disease. Dependence of survival after irradiation of patients with BM on several chosen factors was analyzed by the acturial analyses. Three univariate analyses methods (Log rank, Breslow and Tarone-Ware tests) and one multivariate analysis method (Cox proportional hazards model) were employed. Variables with significant p-values ($p < 0.05$) at least in one of four actuarial analyses were considered possible risk factors for event.

Results: A complete and partial regression was observed in 294 (73.5%) patients, cessation of growth activity in 77 (19.25%) and local progression in 29 (7.25%). Out of 400 patients, 376 (86.5%) patients died and 54 (13.5%) patients are still alive with minimal follow up period of 10 months. Acute toxicity appeared in 24 (10%) patients (score 3, 4) and late in 11 (4.6%) patients. Median survival for patients with SBM was 9 months and for patients with MBM 6 months. The statistically significant prognostic factors in this series of patients with SBM were: age, status of primary tumor, pretreatment neurological symptoms (NFC), histology (better results for renal cell carcinoma and breast carcinoma), the interval longer then 25 months between diagnosis of primary tumor and SBM and the dose to the tumor periphery (20 Gy and higher). The statistically significant prognostic factors for patients with MBM were: sex, performance status (KF), status of primary tumor, other dissemination outside brain.

Conclusions: Treatment of BM by LGK provided sufficient local control in 93% of patients and the improvement of severity neurological symptoms in 69% pts with SBM and in 54%pts with MBM. The most favorable subgroup with a relatively long life expectancy (for SBM and MBM) was defined as a group with no evident active disease outside brain and without progression of primary tumor.

1272 POSTER

Radiochemotherapy with paclitaxel in malignant glioma: results of a phase II study

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Purpose: In a phase II study, the feasability and outcome of a combined radiochemotherapy appraoch was evaluated in patiets with malignant glioma.

Methods: Radiotherapy was given with 60 Gy in conventional fractionation. Paclitaxel was applied on days 0-3, 14-17, 28-31 of radiotherapy. Paclitaxel was started with 20 mg/m*/d and escalated in 10 mg steps until inacceptable toxicity occurred. Subsequent patients were treated with the previous dose level.

Results: From 1996 to 2001, 46 patients were treated in the protocol. 21 patients had grade III and 25 patients grade IV gliomas. 19 patients had a macroscopically complete resection, 27 patients had an incomplete resection or biopsy only. The treatment was well tolerated with very few subjective side effects. Dose limiting toxicity was leucopenia with grade IV leucopenia occurring at 60 mg/m*/d. Mild allergic reactions occurred in 4 instances. 2 patients developed a thrombosis, one patient a lung embolism. 1 patients developed a fatal pneumonia with a normal white blood count. Median survival for grade III glioma was 17 months, for grade IV glioma 10 months.

Conclusion: Radiochemotherapy with paclitaxel was a well tolerated regimen. There was no convincing improvement in median survival.

1273 POSTER

Fractionated stereotactic radiotherapy without whole-brain irradiation in the management of brain metastases

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Purpose: Fractionated stereotactic radiotherapy (FSRT) combines the accurate focal dose delivery of stereotactic radiosurgery with radiobiological advantages of fractionation. Retrospective series showed local control and survival benefits in patients with brain metastases even when only few fractions are employed. The aim of this study was to analyze tolerance and efficacy of FSRT as single modality treatment.

Materials and Methods: 29 patients (20 men and 9 women, mean age 64 years) with 31 metastases were treated with FSRT at our Institution between July 1998 and February 2001. Eligibility criteria were: histological evidence of extracranial primary cancers, 3 or fewer lesions on MRI examination, maximal diameter 3 cm, performance status less or equal to 2. Histologies were: non small-cell lung cancer (18), colon cancer (5), renal cell cancer (3), breast cancer (2) and melanoma (1). Median volume of metastases was 5.5 cm3 (range 0.8-18.8). Patients were immobilised in a Howmedica Leibinger Gmbh relocatable frame (Freiburg, Germany) using cast material made of self-hardening bandages. The planning target volume provided an additional margin of 2 mm in all directions to account for frame inaccuracies; the target volume was encompassed by and prescribed to the 80% isodose.Twenty-one patients were treated with 2 fractions of 12 Gy and 8 with 3 fractions of 8 Gy, delivered on a 6 MV linear accelerator in routine clinical use with 6 non-coplanar arcs.

Results: Median follow-up period was 11 months (range 2-27 months). Local tumor control (LC) was defined as no increase in the tumor's maximal