8706 ORAL

Characteristics and Outcomes After Whole Brain Radiotherapy for Brain Metastases in a Large International Cohort

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Background: Despite the high incidence of brain metastases (BM) and resultant mortality, large cohort studies of whole brain radiotherapy (WBRT) are limited. This study describes the characteristics of and evaluates factors influencing survival following WBRT for BM in a large international cohort.
Materials and Methods: Radiotherapy records at the Radiotherapeutic Institute Friesland (RIF) (1989–2007), Netherlands, Queensland Radium Institute (QRI) (1992–2008), and Liverpool/Macarthur Cancer Therapy Centres (CTC) (1997–2009), Australia were reviewed. Patients undergoing WBRT and brain re-irradiation were identified. Timing of WBRT as it related to other RT courses was documented. Minimum follow-up was two years. The impact of clinico-demographic factors (age, gender, primary cancer (PC), time to BM from PC diagnosis, WBRT dose and treatment institution) on survival, and death within 4 or 8 weeks after WBRT commencement were assessed. Characteristics of patients re-treated with WBRT were assessed.
Results: Of 71,434 cancer patients assessed [16,623 (RIF), 44,974 (QRI) and 9837 (CTC)], 4180 (6%) patients underwent WBRT for BM. Median age was 62 years (18−93) at WBRT, with 2255 (54%) males.
WBRT was the first, second, and third or subsequent RT course in 2581/4180 (60%), 1295/4180 (30%) and 458/4180 (10%) patients respectively. Most common PC sites with BM were lung 2193 (52%), breast 700 (17%), melanoma 383 (9%) and others 904 (22%). Median time to BM from PC diagnosis was 35 weeks (0–1370). For the QRI and CTC patients, the commonest WBRT regimes were 20 Gy in five fractions (65%) and 30 Gy in 10 fractions (21%) respectively.
Overall, median time to death from WBRT commencement was 14 weeks (0–942) with, n = 584 (14%) and n = 1079 (26%) surviving less than four and eight weeks respectively. Similar proportions of lung (26%), breast (24%) and melanoma (24%) PC with BM survived <8 weeks.
Brain re-irradiation was uncommon [n = 154 (4%): RIF 9 (1%), QRI 135 (5%) and CTC 10 (1%)]. Median time from first to second course of WBRT was 37 weeks (1–358 weeks).
Conclusions: This is the one of the largest international cohorts of BM patients treated with WBRT. Poor survival less than 8 weeks from commencement of WBRT suggests that despite established prognostic indicators, patient selection for WBRT remains challenging.

Poster Presentations (Mon, 26 Sep, 14:00−16:30)
Central Nervous System

8707 POSTER

Expression and Regulation of AC133 and CD133 in Glioblastoma

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Background: The biological significance of CD133 in glioblastoma is controversial. Above all, there is disagreement concerning the proper approach, the appropriate (cell) model and the suitable microenvironment to study this molecule, often leading to inconsistent experimental results among studies.
Material and Methods: In consideration of a primary need to dissect and to understand the CD133 phenotype in glioblastoma, we performed a comprehensive analysis of CD133 expression and regulation in a large set of glioblastoma cell lines (n = 20). Our analysis considered alternatively spliced mRNA transcripts, different protein epitopes as well as varying subcellular localizations of CD133 and explored its regulation under pertinent micro-environmental conditions.
Results: Regardless of the experimental context, CD133 mRNA and CD133 protein could be detected in all relevant types of glioblastoma cell lines. In addition, we detected frequent intracellular CD133 protein accumulations located to the ER and/or Golgi apparatus but unrelated to particular CD133 mRNA splice variants or protein epitopes. In contrast, membrane-bound expression of CD133 was restricted to tumour cells bearing the extracellular CD133 epitope AC133. In the latter, differentiation and oxygen levels clearly impacted on AC133 expression and to some extent also influenced CD133 mRNA and protein expression. Most importantly, however, modulation of AC133 levels could occur independently of changes in CD133 mRNA transcription, CD133 protein translation, protein retention or protein shedding.
Conclusions: Our results suggest that the AC133 epitope, rather than CD133 mRNA or protein, accurately mirrors malignancy-related tumour traits such as tumour differentiation and local oxygen tension levels, and thus corroborate its role as a biologically relevant cancer marker.

8708 POSTER

Intranasal Application of Parvovirus H-1 Leads to Efficient Regression of Rat Glioma

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Background: In previous studies we have demonstrated that the apathogenic rat parvovirus H-1 (H-1PV) is capable to induce regression of advanced symptomatic rat and human gliomas in a rat model by applying either intracranially or intravenously. Here we analysed whether *intranasal* inoculation of H-1PV could also be used for efficient virotherapy of experimental glioma.
Material and Methods: In the animal model, rat (RG-2) or human (U87) glioma cells were grafted stereotactically in the brain of rats. After development of tumour visible by MRI, animals were intranasally infected with H-1PV. Control animals received noninfectious virus or PBS.
Results: Single *intranasal* instillation of H-1PV was sufficient to induce an efficient regression of RG-2 cell derived glioma in a rat model, leading to significant prolongation of survival. It was demonstrated that the parvovirus H-1 reached brain and other tissues, and that viral replication-associated regulatory proteins were exclusively expressed in the tumour tissue.
Conclusions: In view of an ongoing study on the use of H-1PV for oncolytic virotherapy, the option of applying the virus intranasally may be a valuable alternative to other routes of infection.

8709 POSTER

Everolimus Inhibits Meningioma Cell Growth in Vitro

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Background: Meningiomas are frequent intracranial tumours. Therapeutic options are limited to surgery and radiation. For the treatment of recurrent or unresectable meningiomas, additional treatment options are needed. We have previously detected frequent upregulation of mTOR-associated proteins in human meningiomas. Everolimus has recently received the approval from the European Medicines Agency for the treatment of advanced renal cell carcinoma. It is the 40-O-(2-hydroxyethyl) derivative of Sirolimus and works similarly as an orally administered inhibitor of the mammalian target of rapamycin.
Materials and Methods: Since everolimus inhibits cell viability and growth, we tested everolimus effects on meningioma cells using MTT- and BrdU assay, and FACS analysis following propidium iodide staining.
Results: The MTT assay indicates the viable cell number by quantifying the activity of enzymes that reduce (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide. For this and all other assays we used a benign (BenMen-1) and a malignant (IOMM-Lee) meningioma cell line. After treatment with 1 and 2 μM everolimus for 24 hours, cell viability decreased to values of about 80% or 70% in both cell lines. Following incubation with 10 μM of the drug, a viability decline to values around 50% was observed, suggesting an IC_{50} around 2 μM for this short term application in both cell lines. The rate of DNA-synthesis (proliferation) in treated cells was determined by standard BrdU assay. The lower concentrations (1−2 μM) elicited a decrease in BrdU incorporation to values of 80% or 70% of untreated controls, again independent from the cell line used. Cells treated with the high concentration level (10 μM) retained only 20% of BrdU incorporation compared to controls. These data demonstrated a dose-dependent antiproliferative effect, which warrants analysis of tumour growth inhibition in a nude mouse model, which is established in our laboratory. FACS analyses of propidium iodide stained cells revealed a regular distribution over the cell cycle phases without hints for G1-arrest, 24 h after treatment. FACS experiments with prolonged incubation periods will follow to allow enhanced G1-accumulation of cells in case of a cell cycle arrest.
Conclusion: Our data clearly indicates that meningioma cells are responsive to everolimus treatment.