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Microcarriers enhance the efficacy of PA317/HSV-1 tk gene therapy in 9L rat glioma model

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Glioblastoma accounts for 1/3 of primary brain tumors. Despite the use of combinations of therapeutic modalities (surgery, chemotherapy, radiation), prognosis is poor, with a median survival of one year and a 9% five-year survival rate. Protocols utilizing viral vectors to deliver a gene for the treatment of malignant gliomas have been developed, and some are in clinical trials. Retrovirus carrying herpes simplex virus tk gene in combination with ganciclovir represents one approach. To improve productivity of retrovirus in vivo, intratumoral injection of retrovirus-producing cells has been used. This approach relies on survival of virus-producing cells in the tumor following injection. Attachment of cells to microcarriers (MC) has previously been shown to increase their survival and function after implantation in Parkinson's disease studies. We therefore tested the effects of MC on HSV-1 tk/ganciclovir gene therapy in the 9L rat glioma model, using PA317 cells carrying a retroviral vector expressing tk gene. Young adult Wistar rats received intrastriatal injections of 5×10^4 9L glioma cells. On day 10 after tumor implantation, 5ul of PBS, PA317 cells (1.8×10^4), or PA317 cells attached to MC (1.8×10^4 cells plus 250ug MC) were injected intratumorally to randomly-divided animals (n = 8 per group). Starting 15 days following tumor implantation, all animals received 25mg/kg ganciclovir i.p. daily for 10 days. Results show that treatment with PA317 cells and ganciclovir had a weak therapeutic effect compared to PBS control group, showing a slightly extended mean survival time (29±1days vs 25±1 days, p=0.0498). MC-attached PA317 cells significantly increased the mean survival time from 29±1 days for PA317 cells only to 48±5 days for MC/PA317 cells (p=0.0052). In addition, approximately 50% of animals treated with MC/PA317 cells survived over 60 days tumor-free while 100% mortality was observed in PBS and PA317 only groups. These results suggest that attaching tk-expressing cells to MC significantly enhanced efficacy of gene therapy for intracranial glioma model, and that MC may represent a general method for enhancing gene therapy to the brain. We are currently using immunocytochemistry to measure life span of implanted PA317 cells by pre-labeling with BrdU, and examining immune response of host animals with or without MC. Possible mechanisms of the enhanced effect of cells attached to microcarriers will be discussed.

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The dose-volume interaction in adult supratentorial low-grade glioma: higher radiation dose is beneficial among patients with partial resection

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Purpose: To test the hypothesis that adult patients with supratentorial low-grade glioma (LGG) and partial surgical resection (PR, ≤ 50% resected) benefit from higher doses of radiation.

Methods: Patients treated with immediate post-operative radiation for WHO grade I-II LGG at the University of Western Ontario between 1979-2001 were studied. Distribution of patient characteristics was compared among those receiving PR and those obtaining subtotal/total resection (STR, > 50% resected). Age > 40 yrs, gender, duration of symptoms > 30 days, seizures at presentation, Karnofsky performance status (KPS) < 70, astrocytoma pathology (AS), and radiation dose ≤ 50 Gy were compared. A Cox regression model was constructed among patients with partial resection to test the influence of radiation dose. Subsequently, a similar model was constructed of the entire patient sample.

Results: One hundred and seven patients were analyzed. Patients who had PR were not significantly different from those with STR when age, gender, symptom duration, seizures, KPS, pathology, or median radiation dose were considered. Among the PR group, 69% had AS histology (N=41), 39% were > 40 years age (N=23) and 29% received ≤ 50 Gy (N=17). Seven patients in the PR group received doses < 42 Gy. Median survival (MST) of patients who received doses ≤ 50 Gy and PR (N=19) was 16.5 months while those who received doses > 50 Gy with PR had a MST of 109.2 months. A Cox regression model of patients with PR was highly significant with radiation dose influencing survival (OS) after controlling for age and histology (p=0.005). Subsequent modelling of the entire group (PR+STR) was completed. The interaction of radiation dose and residual tumour volume was tested after controlling for age and histology. The regression model was highly significant for both OS and PFS (p=0.013 and p=0.003 respectively). The model remained significant after patients receiving doses < 42 Gy (N=7) were excluded (OS p=0.024, PFS p=0.001).

Conclusions: Outcome for adult LGG is highly dependent on post-surgical tumour volume and radiation dose. Patients with partial resection should be considered for higher radiation dose schedules (> 50 Gy). Subgroup analysis of EORTC and RTOG- NCCTG-ECOG dose-response trials seems warranted.

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Telomere length as a prognostic marker in glioblastomas

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Although glioblastomas multiforme are amongst the malignant human tumours with poor prognosis considerable differences do occur between the length of survival for patients with this disease. This suggests the presence of intrinsic factors that may influence outcome. Unfortunately at present the molecular basis of this variation is not known and there are no markers for identifying the 10 to 15% who are deemed 'long term survivors'. Telomeres are essential structures at the ends of chromosomes which are eroded during cell division. Telomere shortening is viewed as a tumour suppressor mechanism which has to be overcome if cells are to become immortal. The objective of this study was to determine the effect of telomere length and maintenance on survival in patients with high grade gliomas. We studied glioblastomas from 30 patients for telomere length and telomerase activity. We found a subset of nine glioblastomas with very long telomeres, a hallmark of the Alternative Lengthening of Telomeres or ALT phenotype while 21 patients had non-ALT tumours. Median survival time for all 30 patients was 357 days (95% CI 244 - 470). Patients with ALT gliomas had a mean post operative survival of 647 days compared to 327 days for patients with 'normal' telomeres treated similarly (p=0.05). 67% of patients with ALT glioblastomas are 'long term'survivors. Patients with telomerase positive tumours had a significantly shorter survival time than those with telomerase negative tumours (257 vs. 411 days p=0.05). We suggest that telomere length and maintenance mechanisms may have a bearing on prognosis for patients with glioblastomas.

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Occupational risk factors for brain tumours in adults. Results from the international brain tumour case- control study

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Purpose: Risk factors for brain tumours have been discussed for various occupational exposures frequently with inconsistent results. The presented study provides the opportunity to further evaluate the etiologic role of occupation for glioma and meningioma.

Methods: A population-based case control study was performed in the late 1980's in eight study centres in Australia (Adelaide, Melbourne), Canada (Winnipeg, Toronto), Europe (France, Germany, Sweden) and USA (Los Angeles). 330 meningioma and 1178 glioma cases, all histologically confirmed, were included. Controls have been individually matched by 5-year age group, gender and region (1123 controls for meningioma and 1987 controls for glioma). Lifetime occupational history was obtained from all cases and controls. Occupational activities were coded by means of ISCO and subsequently grouped into 16 occupational categories. Six of these categories were examined, because of a priori determined hypothesis, initiated by respective literature: chemical, metal, electrical, agricultural, construction and transport. For each tumour type a pooled analysis was performed separately, using conditional logistic regression to estimate relative risks (RR) and 95% confidence intervals (CI) (adjusted for years of education).