Materials and Methods: We examined bone marrow and peripheral blood specimens of 47 patients with newly diagnosed and relapsed PCNSL using PCR for the presence of clonally rearranged IgH genes. The applied IgH PCR method was developed by a European Concerted Action (BIOMED-2). To all samples (50 ng DNA), 3 different FR primer sets (FR1, FR2 and FR3) were applied in conjunction with a JH consensus primer (JH22). Baseline routine staging procedures showed no evidence of systemic lymphoma manifestations in all patients.
Results: In two patients, bone marrow aspirates and/or blood samples showed the same dominant PCR products as in the tumor biopsy specimen, indicating the presence of the same tumor cell population in the CNS as well as in extracerebral sites. Three additional patients had dominant amplificates detected in blood or bone marrow different from the brain tumor specimens that might represent the second rearranged allele of the tumor cell population. To date, one patient has relapsed systemically in the gastrointestinal tract. In this patient, the same clonal IgH rearrangement could be demonstrated in CNS, blood and the systemic relapse.
Conclusions: Extracerebral disease not detectable by routine staging may be present in PCNSL patients. This finding may have an impact on the understanding of PCNSL pathogenesis and the extent of staging and treatment. Patients with subclinical systemic disease may present with unusual sites of systemic relapse.

8701 ORAL

Replication and excretion of parvovirus H-1 in a rat model on oncolytic virotherapy of glioma

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The rodent parvovirus H-1 (H-1PV) is non pathogenic for its natural host but was shown to exhibit anti-tumor activity. H-1PV can infect human cells with a selective cytotoxicity for transformed cells while being innocuous for normal cells. Therefore this virus is currently being assessed for its possible use as an oncolytic agent for virotherapy of glioma, notably since human glioma cells in culture were found susceptible to the killing effect of H-1PV. In a rat model with gliomas established from RG-2 cells, treatment with H-1PV resulted in complete remission of advanced tumors without any side effects.
In preparation of a clinical trial of virotherapy with H-1PV, we analyzed replication of virus in tissue (brain tissue and glioma) in the above rat model, as well as excretion of virus from infected animals.
We could demonstrate synthesis of infectious progeny virus in glioma bearing brain tissue of animals infected with H-1PV intratumorally (intracranially), but not in brains of infected animals that were not bearing tumors. In tumor brains, the titer of virus was 100- to 1000-fold increased within 2 days after infection compared with brains of control animals. This shows virus replication being restricted to tumor tissue.
To address the issue of virus excretion/shedding, body fluids and excretions from animals infected with H-1PV by intracranial or i.v. routes, were assessed by quantitative PCR and infectivity assay for the presence of virus, 14 days after infection. Paralleling results with other animal parvoviruses, infectious virus was demonstrated most frequently in urine samples.
The data demonstrate that therapeutically injected H-1PV is able to replicate in tumor cells, thereby increasing viral amounts may render oncolytic activity more efficient. If confirmed in humans, virus shedding from urine may reduce concern of contamination of personnel in a clinical trial with H-1PV.

8702 ORAL

Methionine PET of (pseudo) tumour progression after stereotactic radiotherapy/ radiosurgery of brain tumours; differential diagnosis of radiation necrosis and tumour recurrence

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Background: Following radiosurgery/stereotactic radiotherapy (SRS/SRT) of primary and secondary brain tumours, differentiation between radionecrosis and recurrent tumour in case of increasing abnormalities on MRI may be difficult. The purpose of this study was to determine the added value of Methionine PET (MET-PET) to MRI in the differentiation between radionecrosis and recurrent tumour and to assess the prognostic value with regard to clinical outcome.
Material and Methods: Scheduled MRI follow up of 12 patients after SRS/SRT(glioblastoma n = 2 meningioma n = 2 and metastases n = 9) showed increase in gadolinium (GADO) high signal areas outside the original tumour area. MET-PET was performed at the time of radiological progression and was co-registered with the MRI at the time of progression and the MR before progression in BRAIN LAB IPlan image 4.1®. The area of progression was determined by subtracting the GADO+ area of the tumour at SRS/SRT at baseline from the GADO+ area at progression. Maximal standard uptake value of MET-PET of this area, original tumour area and SUV max of the contralateral normal hemisphere were calculated. Ratios of SUVmax of the progression area or original tumour area over SUVmax of the normal brain were calculated (SUVpa/nb and SUVot/nb, respectively). Two groups of patients were defined depending on clinical outcome after (pseudo) tumour progression.
Results: Clinical outcome was defined as good (n = 5) if patients remained alive, neurologically stable after MET-PET and additional follow up scans showed regression or no further progression. Outcome was defined as poor (n = 7) if patients showed progressive neurological decline, died (n = 5), showed progressive changes extending into distant normal brain on MRI (n = 1), or showed vital tumour at craniotomy (n = 1). In good outcome patients, the mean SUVpa/nb was 0.95 (min 0.68 max 1.1) versus 1.34 (min 0.90 max 1.68) in poor outcome patients. SUVot/nb were 1.18 (0.60−1.78) and 1.24 (0.52−1.77) in good and poor outcome respectively. SUVpa/nb correlated significantly (Pearson −0.65 p = 0.02) with outcome whereas SUVot/nb did not (Pearson −0.080 p = 0.80).
Conclusions: Low MET-PET SUVmax of progression area after SRS/SRT was correlated with good outcome and likely represents radionecrosis whereas high MET-PET SUV max of the area of progression associated with poor outcome and likely represents true tumour progression.

8703 ORAL

Clinical effect of hypo-fractionated high-dose irradiation on local control of glioblastoma owing to the status of MGMT promotor methylation

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Backgrounds: Our hypo-fratctionated high-dose irradiation (HdI; 68 Gy/8F) showed excellent local control and, with prophylactic intrathecal chemotherapy, significant survival benefit in glioblastoma (GBM) pts. However, it also increased the risk of radiation-induced brain damage in long survivors. MGMT is a DNA repair protein which plays an important role in resistance to anti-cancer treatments. This protein is induced by cytological stresses including irradiation, but its expression level is depending upon the status of MGMT promotor methylation (MGMT-met). The aim of this study is to clarify the significance of MGMT-met as a predictor of radioresistance of GBM and possibility to select pts who really require HdI.
Materials and Method: Histologically confirmed 106 GBMs were enrolled. Among these pts, 56 pts were treated by HdI and 50 were by conventional radiotherapy (cRT; 60 Gy/30F). The status of MGMT-met was determined by methylation specific PCR. Pts were classified into four groups owing to the status of MGMT-met and chemotherapeutic regimens as follows: Group A pts (n = 34) were MGMT-met(+) treated by PAV (procarbazine, nimustine, vincristine); Group B (n = 37) were MGMT-met(−) treated by PAV; Group C (n = 13) were MGMT-met(+) treated by TMZ (temozolomide); and Group D (n = 22) were MGMT-me(−) treated by TMZ. The progression-free survival time (PFS) of pts were compared between HdI and cRT in each groups.
Results: The PFS of pts treated by HdI was significantly longer than those by cRT in both the MGMT-met(+) (p = 0.001) and (−) pts (p = 0.0004), indicating that we can not determine the necessity of HdI by the status of MGMT-met alone. Pts treated by HdI showed significantly longer PFS in Group A (p = 0.003), B (p = 0.047), D (p = 0.0006) but not in Group C (p = 0.141). These results demonstrated that MGMT-met is a predictor of efficacy of TMZ but not PAV, even though PAV also includes alkylating agents. In MGMT-met(−) cases, concurrent effect of HdI and TMZ was observed. The superiority of HdI to cRT was not observed in MGMT-me(+) pts treated by TMZ, and decreased dose of irradiation might preserve the QOL of these pts while keeping the same effect on local control.
Conclusions: HdI was effective regardless of the status of MGMT-met. However, TMZ showed significant effect on MGMT-met(+) GBMs and decreased dose irradiation with TMZ for these pts might be recommended to keep their QOL.