activity was decreased with increasing the concentration of aminotriazole (ATZ; 0.1, 1, 10 mM) dose-dependently. ROS was increased with ATRA and it was augmented by the combination with radiation. ATZ decreased ROS production and increased cell survival by ATRA alone or ATRA combined with radiation despite the reduction of catalase. The catalase that is induced by ATRA increases ROS production and radiosensitivity, and excess catalase would be one of the mechanisms for antiproliferaive effect of ATRA.
This study shows new mechanism of antiproliferaive effect of ATRA and will give a basis for cancer treatment in using ATRA alone or combined with radiation therapy through the elucidation of the role of antioxidant enzymes.

513 POSTER

Erythropoietin in patients with malignant extradural spinal cord compression: functional and pharmacokinetic outcomes

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Background: Erythropoietin has shown neuroprotectant properties in preclinical and randomized studies. There have been no studies showing that erythropoietin enters the central nervous system in patients with extracranial disease.
Methods: Ten paraparetic patients with malignant extradural spinal cord compression who were eligible for radiotherapy, lumbar puncture and intravenous epoetin alfa were enrolled. Patients received epoetin alfa 1500 U/kg intravenously over 30 minutes followed by a standardized dexamethasone and radiotherapy protocol. A lumbar puncture and venipuncture were performed 24–30 hour post-epoetin alfa infusion. Patients were followed daily during radiotherapy, at weeks 2, 3, 4, 8, 12 and at months 6, 9 and 12.
Results: There were no apparent acute toxicities from the epoetin alfa infusion. Erythropoietin was detectable (range 17–214 mIU/ml) in the cerebrospinal fluid in all 8 patients sampled. Before treatment, 8 patients were non-ambulatory and 2 patients were weak but ambulatory. After treatment, 6 (75%) and 2 (100%) recovered or maintained ambulation and improved at least one functional class after a median time of 15 and 18 days, respectively. Five of seven patients with objective sensory deficits and one of seven catheter-dependent patients recovered. Fifty-five percent had a complete pain response and 22% had a partial response. Eight patients have died with a median survival of 1.5 months.
Conclusions: After an intravenous infusion of epoetin alfa, radiotherapy and steroids, high concentrations of erythropoietin were detectable in the cerebrospinal fluid. Patients with malignant extradural spinal cord compression demonstrated encouraging improvements in neurologic function and pain.

514 POSTER

Combined treatment of experimental gliomas with radiotherapy, radiosensitizing and chemosensitizing gene therapy

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Background: The aim of this work was to improve the chemotherapeutic and radiosensitising effects of gemcitabine. Our hypothesis was that increasing the deoxycytidine kinase (dCK) enzyme level that activates gemcitabine within the cells, will lead to increased gemcitabine effects, which could improve the efficacy of chemo- and radiotherapy.
Material and methods: Murine Gl261, rat C6 and 9L and human U373 glioma models were used. The dCK gene was cloned into an adenoviral vector (Ad-dCK). For in vitro proliferation assay cells were transduced with Ad-dCK, treated with Gemcitabine and irradiated. Subcutaneous Gl261 tumors were established in C57BL/6 mice using either wild type or Ad-dCK infected tumor cells. Tumor bearing mice were treated with intraperitoneal injection of Gemcitabine and local tumor irradiation. Tumor growth and survival were followed.
Results: Strong differences were seen in the basal dCK activities of the different glioma cell lines: the murine Gl261 cells showed ten fold higher enzyme activities, than the human and rat glioma cell lines. Intracellular dCK activity was raised by infecting the cells with increasing multiplicities of infection (MOI) of Ad-dCK. Ad-dCK at high MOI was very toxic for Gl261 cells, but did not affect the viability of the other glioma cell lines. The in vitro data showed that increased dCK enzyme activities could not further increase gemcitabine toxicity in Gl261 cells, but gemcitabine itself had a minor radiosensitizing effect. On the contrary, in rat C6 and 9L glioma cells elevated dCK levels could substantially improve both gemcitabine toxicity and the radiosensitising effect. In the case of Gl261 cells, in vivo data are in concordance with the in vitro data: although the combined effect of gemcitabine and radiotherapy has a pronounced synergistic effect (60% tumor free animals after 100 days) compared to mono-therapies (no tumor free animals), increasing dCK levels in the tumor cells did not affect tumor growth or survival. Experiments with C6 and 9L rat models are undergoing.
Conclusions: In the Gl261 model increasing intracellular dCK levels could not improve the chemo- or radio-sensitizing effect of gemcitabine. In the C6 and 9L models elevated dCK levels could increase both the chemo- and radio-sensitizing effect of gemcitabine.

515 POSTER

Potential interest in integrating functional MRI (f MRI) in high-precision RT planning for WHO grade 2 unfavorable and grade 3 supra-tentorial gliomas: first experience with 10 consecutive patients

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Introduction: Among new imaging techniques potentially useful in radiotherapy (RT) of patients (pts) with brain gliomas, fMRI is supposed to add informations to conventional MRI (cMRI). fMRI could modify Gross Tumor Volume (GTV) delineation, visualize inside a low-grade glioma small focuses of higher activity (for an RT boost) and identify sites essential for memory and language, to be eventually avoided, these functions being potentially altered by RT. Here, fMRI was evaluated for adults with gliomas of intermediate prognosis, in addition with computed tomography (CT) scan and cMRI, routinely used for RT planning (RTP). The main goal was to evaluate if fMRI could modify CT/cMRI-based RTP.
Description: After biopsy/surgery, 10 adult pts with gr. 2 unfavorable or gr. 3 supra-tentorial glioma were entered in the study. CT scan and cMRI (T1 Gado, T2-weighted sequences) were performed in RT position. fMRI was subsequently performed in the same position using 1) a diffusion tensor imaging (DTI)-based fiber tracking technique, visualizing major white matter tracts, 2) a perfusion-weighted imaging identifying higher perfused areas, 3) cortical activation with memory and language paradigms.
Firstly, only CT scan and cMRI were used for RTP, contouring of GTV was based on T1 Gado for gr. 3 and T2 for gr. 2 gliomas, organs at risks (OaR) were delineated. Then, RTP was made, optimizing GTV coverage and mimimizing irradiation of OaR. Pts were treated according to the conventional RTP and baseline neurocognitive functions were evaluated before RT, then bi-annually.
Secondly, fMRI images were analysed and used to define a "functional" GTV for comparison with the conventional one.
Results: 10 adult pts (mean age of 42 yrs) were included in 6 months, all with an oligodendroglioma component. First symptom was epileptic seizure in 8 pts. In 6 pts, glioma was located in the left-temporal area with a mean size of 6 cm in T2-cMRI, 6 showed a mild signal enhancement. In 7 pts, highly active focuses were identified, within homogenous T2 hypersignal areas. In 5 patients, DTI fiber-tracking showed warped white matter fibers, strongly suggesting brain infiltration beyond cMRI images. Overall, the balistic of RT could be potentially modified in 4 pts.
Conclusion: The preliminary results of this study strongly suggest that the entire spectrum of fMRI can play a major contribution to improve the accuracy of high precision RT in adult pts with non-glioblastoma gliomas.

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p53 and RB suppressor pathways deregulation by HDM2 overexpression in human meningeal hemangiopericytomas. double immunofluorescence and laser scanning confocal microscopy study.

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Meningeal hemangiopericytomas (MHPC's) are slow growing tumors, that in spite of complete surgical removal followed by radiation, recur and

metastasize outside de CNS. The retinoblastoma (Rb) tumor suppressor gene is a negative cell-cycle regulator. Hypophophorylated Rb protein (pRb) binds and inactivates the E2F1 transcription factor regulator of DNA synthesis. However, mitogens, trigger cyclins D transcription, and binding to cyclin-dependent kinases (CDKs) 4 and 6, which initiate pRb phosphorylation, completed by cyclin E-CDK2.
Hyperphosphorylated pRb loss growth suppression function, releasing E2F1, leading to DNA synthesis and cell-cycle progression. The p53 gene plays a central role in the stress response to DNA damage and hyperproliferative signals, to prevent the growth and survival of potentially malignant cells. Activation of p53 may induce G1/S cell cycle arrest to allow DNA repair, or in case DNA is irreversibly damaged, can induce apoptosis. p53 & Rb pathways were investigated by Immunohistochemistry detection of (p14/ARF, p53, p21/WAF1, HDM2), (Rb, E2F1, Cyclins D1, D3 and E, CDK4, p16/INKa) protein expression, in 18 MHPC's (11 primary, 4 of them recurrent in 1, 1, 2 and 4 occasions). Double Immunofluorescence (DIF) staining and Laser Scanning Confocal Microscopy (LSCM) was used to address co-localization and molecular interactions. Simultaneous p53 and wild type p53 trans-activated genes (p21/WAF, HDM2) expression occur in all cases. This argues against p53 mutation. HDM2 over expression was observed in 10 cases (55.5%). DIF staining and LSCM displayed HDM2 and p53 co-localization.
This strongly suggests that HDM2 binds and inactivates p53. Rb protein expression was low in 13 cases, negative in four and over expressed in one. Over expression of E2F1 (10 cases), Cyclin E (7 cases), CDK4 (5 cases), Cyclin D3 (2 cases) and Cyclin D1 (1 case) was observed. Low Rb expression and E2F1 over expression suggest impairment of Rb function. Rb and E2F1 co-localization was very weak or negative by DIF&LSCM. This argues that Rb is not binding and inactivating E2F1 and not acting as a suppressor. Moreover, HDM2 and E2F1 co-localization was frequently observed. This strongly suggests that HDM2 binds and activates E2F1.

Publication
Central nervous system

517 PUBLICATION

Tomotherapeutic intensity-modulated radiosurgery: improving dose gradients and maximum dose after inverse optimization using ActiveRx

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Intensity-modulated radiosurgery (IMRS) for brain metastases and AVM using the Nomos Peacock IMRT system has been delivered in >150 cases in our institution over the last 4 years. A new software tool provided within the Corvus planning software allows for post inverse planning re-optimization and individualization of the dose distribution. We analyzed this tool with respect to increasing the steepness of the dose gradient and dose inhomogeneity while maintaining conformity.
Fifteen radiosurgery plans for solitary brain metastases that were clinically delivered during the last two months were analyzed. All plans were copied and ActiveRX, a tool available during plan review, was opened. The toolset in ActiveRX includes an eraser, a pencil to redefine isodose lines and a drag and drop tool, allowing reshaping of isodose lines. To assess changes in the steepness of the dose gradient and dose homogeneity, the 100%, 90%, 50% and 25% isodose volume, the volume of the target, maximum dose and mean dose to the target were sampled.
Target volumes ranged from 0.6 to 14.1 cm^3 (mean/median 3.9/1.8 cm^3). Mean RTOG conformity index (CI) of plans delivered was 1.23±0.31, mean homogeneity index (HI) was 115±5%. Using ActiveRX, the mean CI was slightly improved to 1.14±0.1, with associated increase in HI to 141±10%. The average respective Ian Paddick CI for the 100%, 90% 50% and 25% isodose lines were 0.79 vs.0.83, 0.44 vs. 0.59, 0.12 vs. 0.19, and 0.04 vs. 0.07, with significant improvements using ActiveRx post-optimization.
A post inverse planning optimization tool for IMRS plans allowed for statistically significant improvements in the steepness of the dose gradient, and increased maximum and mean target doses compared to clinically delivered plans that were already considered excellent. Gains were especially pronounced in the reduction of normal brain tissue included into the 90%, and 50% isodose lines. We have since made this process part of the clinical routine for all cranial IMRS procedures.

518 PUBLICATION

The influence of dose and target volume on results of radiosurgery for brain arteriovenousus malformation

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Background: Stereotactic radiotherapy is non-invasive and effective method of AVM treatment. Tumor volume and delivered dose are very important factors limiting effectiveness of radiosurgery.
Material and methods: The retrospective analysis of stereotactic radiotherapy effectiveness for arteriovenous malformation (AVM) was done. 47 cases (27 male 20 female) of brain AVM treated with radiosurgery were analyzed. Mean age was 41. The most frequent tumour location was frontal and parietal lobe. Mean time of symptoms was 54 months. 14 patiens were after neurosurgery (embolization). 90% of patiens were in good performance status (ZUBROD 0 or 1). 12 patiens had significant neurological symptoms. Tumor volume varied from 0.06 to 101 cm (mean 4.6). Mean total dose was 15 Gy and ranged from 7 to 20 Gy. Mean of irradiated fields number was 9. In 42 cases conformal and in 8 cases intensively modulated radiosurgery were used. Tolerance of treatment was acceptable (only 4 patiens had side effects). Median follow up varied from1.3 to 47 months (mean 14.7 Gy). Tumor size and malformation of blood flows based MRI, CT and angioMRI images and neurological status 6, 12, 24 months after RT were assesed. Time to malformated blood vessels obliteration was measured. Correlations between particular assessed parameters were checked using Sperman test. Influence of total dose and tumor volume on treatment results was analyzed using logistic regression test.
Results: The complete tumor regressions (CR) evaluated using MR or CT scans were observed within 6 months in 27% of patiens, in 31% within 12 months and in 50% of patiens within 24 months then radiotherapy completion. Partial regressions (PR) were observed in 41% of patiens 6 months after treatment, in 21% 12 months and in 20% 24 months after radiotherapy. Mean time to partial AVM vessels obliteration was 7.8 months and mean time to complete vessels obliteration was 10.8 months. Overall response rate (CR+PR) was 53%. Spearman analysis showed only nagative corerelation between tumor volume and MR or CT based tumor regression 3 months after RT ($p = 0.03$, $R = -0.35$). Logistic regression revealed that only total dose has negative influence on partial regression ($p = 0.008$), target volume does not infuence on PR. Analysis in subgroups proved this influence only for patiens who delivered total dose less than 16 Gy. Futher logistit regression analysis showed that neither target volume nor total dose has influence on tumor CR and overall regression.
Conclusions: Stereotactic radiosurgery is safe and non invasive modality of AVM treatment, giving 53% of overall responses. Target volume has no influence on propability of tumor regression but delivered dose influences on tumor partial regression.

519 PUBLICATION

Postoperative radiotherapy and chemotherapy in the management of oligodendroglioma: single institutional review of 88 patients

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Background: We retrospectively evaluate the prognostic factors affecting the local control, survival and the potential role of chemotherapy in the management of patients with oligodendroglioma.
Material and methods: The medical records of 88 patients treated by postoperative external beam radiotherapy ± chemotherapy at our institution between December 1993 and December 2002 were analyzed. Nine patients (10%) were treated with an accelerated fractionation scheme, while 79 patients were treated with conventional doses. The median RT dose was 54.8±2.58 Gy for low-grade tumors, and 58.7±2.46 Gy for high-grade tumors. PCV chemotherapy regimen was given to 18 patients; temozolamide was administered in 3 patients. Chemotherapy was not given concomitantly in any patients.
Results: The median follow-up was 56 months (range 7–134 months). The 5-year overall and progression-free survival rates for entire group were 86% and 79%, respectively. Patients with epilepsy at presentation had better 5-year overall survival (93% vs. 74%, $p = 0.04$). High grade tumors had significantly lower overall survival rate. Age, presence of motor deficit at diagnosis and histological grade were found have a significant impact on progression-free survival. The 5-year overall and progression free survival rates of patients with high-grade tumors were 69%, 51% and 74%, 68% for chemotherapy and nochemotherapy group, respectively ($p = 0.9$ for OS, $p = 0.3$ for PFS). In multivariate analysis no significant factor affecting the overall survival and progression-free survival was found.