Title

ACTR-67. A PHASE I STUDY OF CONVECTION-ENHANCED DELIVERY OF LIPOSOMAL-IRINOTECAN (ONIVYDE) USING REAL-TIME IMAGING WITH GADOLINIUM IN PATIENTS WITH RECURRENT HIGH GRADE GLIOMAS: RESULTS THUS FAR

Journal

Neuro-oncology, 20(Suppl 6)

ISSN

1522-8517

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Publication Date

2018-11-01

Peer reviewed

mutant subgroups. CONCLUSIONS: Combined treatment with radiotherapy and chemotherapy resulted in markedly improved TTF in patients with molecularly defined oligodendroglioma and astrocytoma.

ACTR-64. OBJECTIVE RESPONSES TO CHEMOTHERAPY IN RECURRENT GLIOMA DO NOT PREDICT BETTER SURVIVAL: A PROSPECTIVE ANALYSIS FROM THE GERMAN GLIOMA NETWORK

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Outside of clinical trials, the occurrence of objective responses (OR) to chemotherapy in patients with recurrent gliomas is poorly characterized. Further, the predictive value of OR for PFS and OS is unclear. We screened the German Glioma Network Database for patients who had received chemotherapy only for recurrent glioma. As PFS was not available for a large number of patients we used the composite endpoint time-to-treatment-failure (progressive disease, start of a new therapy or death). We included 485 patients who received 646 chemotherapy regimens for treatment of recurrent glioma. Of these, only 32 chemotherapies in 32 patients resulted in an OR (30 PR, 2 CR) after central review according to RANO criteria. OR rates were 2.8%, 11.0% and 10.6% for glioblastoma, anaplastic glioma WHO grade III and diffuse glioma WHO grade II, respectively. Temozolomide (n=232) resulted in ORs in 7.8% of the patients, while nitrosourea (n=212) and imatinib (n=27) resulted in ORs in 6.1% and 3.7%, respectively. Overall, responders showed a significantly improved OS compared to non-responders (median OS 33.3 versus 15 months, p=0.054). Yet, a Cox regression analysis adjusted for diagnosis and age did not reveal a significant association of objective responses with overall survival (relative risk 0.8, p=0.391). In addition, we generated a 1:3 cohort (n=96) of non-responders matched for diagnosis. There was no relevant difference in OS comparing responders to the matched cohort (median OS 33.3 versus 25.6 months, p=0.929). When comparing non-responders with longer time-to-treatment-failure (>14 weeks, assumed stable disease as best response) with responders (n=32) the difference in outcome was lost (median OS 24.3 versus 33.3 months, p=0.86). In this prospective trial ORs to chemotherapy in the recurrent setting were rare. Notably, when comparing responders with a matched cohort or patients with assumed stable disease as best response, ORs were not associated with improved survival.

ACTR-65. INTRATHECAL PEMETREXED FOR PATIENTS WITH RECURRENT LEPTOMENINGEAL METASTASIS FROM LUNG ADENOCARCINOMA: A PHASE I CLINICAL TRIAL (IPRLM,NCT03101579)

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BACKGROUND: To determine toxicities, maximally tolerated dose (MTD), and potential antitumor activity of intrathecal pemetrexed (IP). MATERIAL AND METHODS: Pulmonary adenocarcinoma patients with recurrent or progressive leptomeningeal metastases (LM) after intrathecal chemotherapy and other LM-related therapy were included. IP doses escalated from 10 mg to 15 mg, and even 20 mg. Protocol schema of IP was twice per week for 2 weeks (induction therapy), followed by once per week for 2–4 weeks (consolidation therapy). The primary endpoints were MTD and safety. The secondary endpoint was efficacy. Plasma and cerebrospinal fluid (CSF) samples were collected and analyzed for drug concentration. RESULTS: Nine patients (male: 3; female: 6; age: 37–71 years; median: 55) were enrolled between March 2017 and March 2018. All cases received total 50 times of IP (2–8 times, median: 6). Incidence of >grade III adverse events was 50%, including 4 cases with hematological toxicities and 2 with radiculitis. One patient received 15 mg IP dose expired due to hematological toxicities. Then protocol was revised. The dose was decreased to 10 mg. B12 and folic acid supplementation was indispensable. Three more cases were enrolled subsequently. No case showed severe hematological toxicities. Total clinical response rate was 80%. For the cohort of 10 mg dose, clinical response rate was 88%. All cases were followed up until May 1, 2018. Six cases died from cancer or related complications. No acute or subacute CNS toxicity was observed. The median overall survival was 2.5 (0.3–12) months from enrollment of this study. Pemetrexed was not cumulative in CSF. Times of plasma concentration peak were 6 h in 3 cases, 9 h in 1 case, and 12 h in 1 case after IP. CONCLUSION: Pemetrexed is suitable for intrathecal use. A dose of 10 mg shows well safety and high clinical response rate, which is worth for subsequent trials.

ACTR-66. BEVACIZUMAB THERAPY FOR THE TREATMENT OF ADULT GLIOBLASTOMA: SYSTEMATIC REVIEW & META-ANALYSIS

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INTRODUCTION: Glioblastoma is the most common high-grade primary brain tumor in adults. Standard multi-modality treatment of glioblastoma often results in transient tumor control, but inevitably gives way to disease progression. The need for other therapeutic avenues led to interest in the anti-angiogenic therapy, namely bevacizumab, as a treatment for glioblastoma. We sought to determine the efficacy of bevacizumab as a treatment for glioblastoma. METHODS: We conducted a literature search using the PubMed database and Google Scholar to identify randomized controlled trials (RCTs) since 2014 investigating the safety and efficacy of bevacizumab in the treatment of adult patients (18 years and older) with both newly diagnosed and recurrent glioblastoma. Only Level I data that reported progression-free survival (PFS) and overall survival (OS) were included for analysis. RESULTS: We identified 14 studies that met our criteria, reporting on a total of 3,192 patients. Our preliminary analysis finds that treatment with bevacizumab consistently prolongs PFS with a correspondent decrease in PFS hazard ratio (HR) for treatment groups that include bevacizumab versus those that do not. Bevacizumab had no significant effect on OS in patients with newly diagnosed or recurrent glioblastoma. Seven studies reported on MGMT status: four studies found that patients with methylated MGMT status had a consistently longer PFS and OS, corresponding with significantly lower HR for both variables, when compared to unmethylated groups. CONCLUSIONS: Our preliminary findings suggest that bevacizumab therapy is associated with a longer PFS in adult patients with glioblastoma, however, bevacizumab had an inconsistent effect on OS in this patient population. The differential response to bevacizumab in relation to MGMT methylation status and molecular subtype requires further analysis.

ACTR-67. A PHASE I STUDY OF CONVECTION-ENHANCED DELIVERY OF LIPOSOMAL-IRINOTECAN (ONIVYDE) USING REAL-TIME IMAGING WITH GADOLINIUM IN PATIENTS WITH RECURRENT HIGH GRADE GLIOMAS: RESULTS THUS FAR

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BACKGROUND: Chemotherapy for high grade gliomas (HGG) is limited by the blood-brain-barrier (BBB). Convection enhanced delivery (CED) improves chemotherapy delivery by utilizing fluid convection obviating the challenges of crossing the BBB while minimizing systemic toxicity. CED of nanoliposomal-irinotecan (Onivyde) showed to be a superior delivery route for anti-tumor activity in animal models. An advance of this trial is the development and use of real time CED, which utilizes MRI to visualize the CED process with the aid of co-convected contrast agents, monitoring delivery into the brain and affording for corrective action. METHODS: This is a 3 + 3 single dose escalation trial with 2 cohorts: 20mg/ml and 40mg/ml. Onivyde and GAD were co-infused via the same catheters in a one-time delivery. The total volume of infusate, and consequently total dose, were personalized based on the patient's tumor volume, and ranged from 20–680 mg of Onivyde, given via up to 4 catheters. Tumor diameters were allowed to be 1 – 4 cm, with injection volumes ranging from 2 – 17 mL of infusate. RESULTS: 10 patients have been treated on this protocol, all in under 5 hours. There were 7 GBs, 2 anaplastic astrocytomas, and 1 oligoastrocytoma. Seven patients lived

over a year after treatment, which is remarkable since median survival rates for multiply recurrent: GBs = 8 months, AAs = 11 months. Utilizing imaging software, we correlated pre-infusion modeling of the drug distribution with post-infusion imaging. A number of technical challenges were overcome by real time monitoring; the total volume of distribution (Vd), and the Vd to volume infused (Vi) ratio for each infusion was ~2. CONCLUSIONS: Image-guided distribution allows for safe real-time placement and adjustment of CED cannula of Onivyde into patient's brains. Such methods allow for maximum tumor coverage and warrant further studies with repeat dosing.

ACTR-68. INITIAL TREATMENT OF GBM WITH A KETOGENIC DIET ALONG WITH RADIATION AND CHEMOTHERAPY: FEASIBILITY, TOXICITY AND RESPONSE

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INTRODUCTION: We initiated and now report early outcomes of a pilot clinical trial study using a ketogenic diet (KD) combined with radiation and chemotherapy as initial therapy for aggressive gliomas (glioblastoma, GBM). METHODS: Eligibility criteria included: 1. Tissue diagnosis; 2. Age over 18; 3. ECOG performance status of 2 or better; and 4. Not having diabetes or being pregnant. An isocaloric KD diet with 3:1 weight ratio of fat to combined weight of carbohydrate and protein was supervised by an experienced dietitian. Per protocol the KD together with radiation and chemotherapy was maintained for 6 weeks. RESULTS: 9 patients (mean age 45, 8F,1M) completed 6 weeks of this trial. Blood counts, chemistries, lipid profiles and uric acids were not markedly changed. No other significant side effects were observed. Ketosis was maintained for the 6 week study period with blood ketone and glucose levels checked twice daily: The ketones ranged between 0.9 and 4.1 and glucose ranged between 80.3 and 120. Patients' daily AM weights decreased on average < 10% during the study. 3 patients (mean age 28) showed no progression of their gliomas at 34 (IDH +), 19 (IDH +), and 25 (IDH WT) months since diagnosis. 6 patients (mean age 54) have died at 25, 25, 13, 12, 9 and 9 months after diagnosis. CONCLUSIONS: 1. Combining an adjuvant KD with standard therapy of radiation and chemotherapy right after tissue diagnosis is feasible and safe. 2. Daily measurements of blood ketones and glucose are necessary to assure continued ketosis; 3. KD may be a helpful adjuvant initial treatment of GBM patients, especially in younger patients. A larger study will be required to test this hypothesis.

ACTR-69. BLOOD DERIVED EXOSOMAL hTERT mRNA - A POTENTIAL BIOMARKER FOR GLIOBLASTOMA

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BACKGROUND: Primary glioblastoma multiforme (GBM) have a high proportion (~80%) of TERT-expressing tumors, indicating that this is the primary mechanism of telomerase (hTERT) activation. Exosomes are nano-sized secreted vesicles containing nucleic acids and proteins, which reflect the content of the mother cells. We have previously shown that hTERT transcripts in serum exosomes may serve as a "pan-cancer" diagnostic method, reflecting the load of hTERT in systemic cancer cells. The goal of the current study was to evaluate whether exosomal hTERT may serve as a circulating biomarker for GBM. METHODS: hTERT mRNA levels were determined in serum derived exosomes obtained from 20 GBM patients and 45 healthy controls. The level of exosomal hTERT mRNA was measured prior to surgery in all GBM patients. In 10 patients additional longitudinal evaluation was performed in blood samples obtained prior to and after concurrent radio/chemotherapy and again during adjuvant temozolomide treatment. RESULTS: Circulating hTERT transcripts were absent in controls and were variably detected in 40% of GBM patients with significantly elevated mean level at diagnosis (p=0.049). These transcripts were gradually downregulated on longitudinal evaluations and during treatment period with significant reduction observed after 3 months of adjuvant treatment when compared to initial sampling (p=0.026). In 10 patients an analysis of *hTERT* promoter mutation was performed and in 8/10 one of the two common mutations (C228T and C250T) was detected on tumor samples. CONCLUSIONS: hTERT mRNA levels may reflect the tumor burden and the clinical status of patients with GBM. In systemic tumors exosomal hTERT mRNA expression is detected in about 60% of cases while in GBM the percentage is probably lower. In patients with detectable levels, this assay may serve as a serum biomarker. These results warrant further confirmation and an update on an extended cohort of patients will be presented at the meeting.

ACTR-70. INCREASING SURVIVAL IN BIOPSY-ONLY GBM PATIENTS

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It is generally expected that survival from GBM is correlated to the extent of resection. That is, patients having only a biopsy don't live as long as those having partial or complete resections. Fifteen years ago, 2-year survival of biopsy-only patients was 5%. In 2005, Stupp *et al.* added temozolomide (TM Z) to radiation therapy and also established a follow-up TMZ chemotherapy regimen. This increased 2-year survival of unresected GBM patients from 4.6% to 10.4 % (Stupp et al., 2009). Lately, due to the still-low survival rate, biopsy-only patients are often excluded from GBM clinical trials. It is known that hypoxic tumors are resistant to radiation therapy (Sheehan *et al.*, 2010). Thus, Diffusion Pharmaceuticals Inc. added trans sodium crocetinate (TSC) to temozolomide-radiation therapy, but not to the chemotherapy in a Phase 2 clinical trial (Gainer, *et al.*, 2017). TSC stimulates re-oxygenation of hypoxic tumors (Sheehan, et al, 2009, 2011). It acts systemically to re-oxygenate hypoxic tissue but has no effect on normal cells. When combined with temozolomide and radiation, TSC resulted in a 2-year survival of biopsy-only patients of 40%, in effect quadrupling the 2005 Stoop results. TSC is being currently studied in a Phase 3 GBM trial involving solely biopsy-only patients. In this trial, TSC is added to both the radiotherapy and chemotherapy sessions, preceding the dosing of TMZ. This trial is called INTACT (NCT03393000) and is currently enrolling patients.

ACTR-71. PHASE 1/2 STUDY OF DIANHYDROGALACTITOL (VAL-083) WITH RADIATION THERAPY IN PATIENTS WITH NEWLY DIAGNOSED, MGMT-UNMETHYLATED GLIOBLASTOMA

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Glioblastoma (GBM) is the most common and aggressive primary brain cancer. Current standard-of-care includes surgery followed by chemo-radiation and temozolomide. An unmethylated promoter for O6-methylguanine-DNA-methyltransferase (MGMT) is a validated biomarker for temozolomide-resistance and is strongly correlated with poor outcomes. Unmethylated MGMT represents the majority of newly diagnosed GBM tumors. VAL-083 is a first-in-class bi-functional DNA-targeting agent that has shown activity against GBM in NCI-sponsored clinical trials both as single agent and in combination with radiotherapy. VAL-083 induces interstrand cross-links at N7-guanine, leading to DNA double-strand breaks and cell-death. VAL-083s unique mechanism-of-action circumvents MGMT-mediated chemoresistance, and it has demonstrated cytotoxicity in MGMT-unmethylated GBM cell-lines, cancer stem cells (CSCs) and in vivo models. Furthermore, VAL-083 acts as a radiosensitizer in GBM CSCs and non-CSCs. We completed a dose-escalation trial of VAL-083 in recurrent GBM, and a generally well-tolerated dosing regimen was selected for further clinical development. The present trial is an ongoing open-label, biomarker-driven, Phase 1/2 study to evaluate the tolerability and efficacy of VAL-083 in combination with radiotherapy in newly diagnosed MGMT-unmethylated GBM patients. A treatment regimen, consisting of a 6-week induction period of VAL-083 and concurrent radiation (2 Gy daily, 5 days/week) followed by up to 24 weeks of maintenance therapy with single-agent VAL-083, is being evaluated. The study is being conducted in two parts: 1) a dose-escalation part (20, 30, and 40mg/m2/day IV infusion on days 1,2,3 of a 21-day cycle) in up to 10 patients; 2) an expansion part in up to 20 additional patients at the determined well-tolerated dose. Tumor response will be assessed by MRI, according to RANO criteria. Efficacy endpoints include progression-free survival (PFS) and overall survival (OS). Additional endpoints include safety evaluations and pharmacokinetic assessments of plasma and CSF samples. Enrollment and safety data update will be provided at the meeting. Clinicaltrials.gov identifier: NCT03050736.

ACTR-72. IDH-WILD TYPE GRADE II GLIOMAS: A RETROSPECTIVE SERIES OF ITALIAN ASSOCIATION OF NEURO-ONCOLOGY

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