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Neurosurgery Concepts

Neurosurgery concepts: Key perspectives on dendritic cell vaccines, metastatic tumor treatment, and radiosurgery

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Abstract

Background: This is a laboratory study to investigate the effect of adding brain-derived-neurotrophic factor (BDNF) in a poly (*N*-isopropylacrylamide-*g*-poly (ethylene glycol) scaffold and its effect on spinal cord injury in a rat model.

Methods: This is a laboratory investigation of a spinal cord injury in a rat model. A dorsolateral funiculotomy was used to disrupt the dorsolateral funiculus and rubrospinal tract. Animals were then injected with either the scaffold polymer or scaffold polymer with BDNF. Postoperatively, motor functions were assessed with single pellet reach to grasp task, stair case reaching task and cylinder task. Histological study was also performed to look at extent of glial scar and axonal growth.

Results: Animals received BDNF containing polymer had an increased recovery rate of fine motor function of forelimb, as assessed by stair case reaching task and single pellet reach to grasp task compared with control animals that received the polymer only. There is no significant difference in the glial scar formation. BDNF treated animals also had increased axon growth including increase in the number and length of the rubrospinal tract axons.

Conclusion: BDNF delivered via a scaffold polymer results in increased recovery rate in forelimb motor function in an experimental model of spinal cord injury, possibly through a promotion of growth of axons of the rubrospinal tract.

Key Words: Radiosurgery, Gamma Knife, metastasis, immunotherapy, glioblastoma, dens fracture, meningiomas

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Phase 1 Trial of a Multiepitope-pulsed Dendritic Cell Vaccine for Patients with Newly Diagnosed Glioblastoma.[4]

STUDY QUESTION

Is vaccination of newly diagnosed glioblastoma (GBM) patients with autologous dendritic cell vaccine pulsed with class 1 peptides from tumor-associated antigens (TAA) expressed on gliomas and overexpressed in their stem cell population safe, and does it produce an immune response? (ICT-107 Phase 1 Trial).

Seventeen newly diagnosed GBM patients after >95% resection that were HLA-A1- and/or HLA-A2-positive and expressed at least one of the TAA epitopes HER2, TRP-2, gp100, MAGE-1, IL13Ra2, and AIM-2 were eligible for this Phase 1 trial. TAA contained portions of the antigen called epitopes that are recognized by the immune system. (The designations listed are identified epitopes). The trial also included 3 recurrent GBM patients after gross total resection and 1 brainstem glioma for a total of 21 patients. Mononuclear cells from leukapheresis of these patients were differentiated into dendritic cells, pulsed with all six TAA peptides, and administered intradermally three times at 2-week intervals. Safety, immune responses, and survival were assessed.

Immune response data on 15 newly diagnosed patients showed 33% responders. TAA expression by quantitative real-time PCR (qRT-PCR) from fresh frozen tumor samples showed all patient tumors expressed at least three TAA, with 75% expressing all six. Correlations of increased progression-free survival (PFS) and overall survival (OS) with quantitative expression of MAGE1 and AIM-2 were observed, and a trend for longer survival was observed with gp100 and HER2 antigens. Target antigens gp100, HER1, and IL13Ra2 were downregulated in recurrent tumors from 4 HLA-A2+ patients. A decrease in or absence of CD133 expression was seen in five patients who underwent a second resection. At a median follow-up of 40.1 months, 6 of 16 newly diagnosed GBM patients showed no evidence of tumor recurrence. Median PFS in newly diagnosed patients was 16.9 months, and median OS was 38.4 months.

Perspectives

Despite advances in the treatment of cancer patients and the understanding of glioma biology, the overall prognosis of patients diagnosed with GBM remains dismal. Over the past decade, immunotherapy and targeting the cancer stem cell population have been highly publicized novel treatment strategies for GBM patients. This Phase 1 Trial utilizes a novel immune therapy dendritic vaccine approach that targets cancer stem cell antigens. The treatment was found to be safe, and although the patient numbers are low and nonrandomized, the PFS and median OS numbers are extremely promising. A randomized, double-blind, controlled phase IIb study of the safety and efficacy of ICT-107 in newly diagnosed patients with GBM following resection and chemoradiation is ongoing. Summary written by: Gordon Li, MD. Local disease control for spinal metastases following "separation surgery" and adjuvant hypofractionated or high dose single-fraction stereotactic radiosurgery: Outcome analysis in 186 patients.[3]

QUESTION

What is the role of "separation surgery" in combination with stereotactic radiosurgery (SRS) in patients with high grade epidural spinal cord metastases?

The authors of this study aim to evaluate the role of "separation surgery" followed by delivery of SRS to the resection bed using either single or hypofractionated treatment doses in patients with metastatic high grade spinal cord compression (ESCC). Separation surgery is defined as surgical decompression such that the tumor is circumferentially resected from the adjacent dura effectively reconstituting the cerebrospinal fluid (CSF) space within the thecal sac. The radiation doses to the resection bed include 24 Gy radiation in a single fraction, high dose hypofractionated SRS ranging between 24 and 30 Gy in 3 fractions, and low dose hypofractionated SRS ranging between 18 and 36 Gy in 5-6 fractions.

The author evaluated 186 patients with a range of radiosensitive and radioresistant tumors all with high grade ESCC. All patients underwent separation surgery followed by SRS 2-4 weeks after surgery. A computed tomography (CT) myelogram was used for radiation treatment planning in all patients. The clinical treatment volume included the entire vertebral body at the involved level up to the dural edge. The overall median follow-up was 7.6 months. Tumor progression was seen in 16.4% of patients at 1 year following SRS for the entire cohort. A significant difference in local control was seen in the single and high dose hypofractionated patients as compared with the low dose hypofractionated patients. Progression at 1 year was seen in 4.1% in the former and 22.6% in the latter, $P < 0.04$. Tumor radiation sensitivity did not significantly correlate with PFS.

The role of separation surgery for patients with metastatic high grade ESCC followed by SRS is an effective treatment algorithm for both preservation of neurological function and local tumor control. The authors displayed a significant difference in 1-year local control rates in patients receiving high dose SRS as compared with the low dose regimen.

Perspective

This study provides validity for a treatment algorithm previously reported by Memorial Sloan-Kettering Cancer Center (MSKCC) with a large patient cohort. This study

provides additional support in a growing body of literature supporting the use of this regimen outside major cancer centers such as MSKCC. In smaller academic institutions and community medicine, radiation oncologists are reticent to deviate from traditional treatment algorithms using conventional external beam radiation therapy with justifiable concern for spinal cord injury. The authors have effectively shown that these patients do not experience radiation-induced spinal cord injury and that the higher radiation doses provide more effective tumor control. Equally important, this study explores the role of circumferential removal of tumor in these patients. In addition, this study displays the importance of a multidisciplinary approach to this patient population. Future prospective studies with longer follow-up and larger cohorts will serve to further validate the results seen in this study. Summary written by: Jonathan H. Sherman MD. Gamma Knife surgery for the treatment of 5-15 metastases to the brain.[5]

QUESTION

How many is too many to treat metastatic brain tumors with Gamma Knife Radiosurgery?

The authors performed a retrospective analysis of 96 patients who have 5-15 brain metastases between 2003 and 2012. The patients were chosen for Gamma knife radiosurgery (GKS) based on magnetic resonance imaging (MRI) and the diagnosis of known primary cancer of variable histology. The primary endpoint was OS from the date of GKS. Statistical analysis was performed to identify prognostic factors related to OS. The patients were categorized as Recursive Partitioning Analysis (RPA) class I and II (no RPA III patient). The median number of treatment lesions was 7 (mean 7.13), the median treatment volume was 6.12 cm^3 (0.42-57.83 cm^3) and the median clinical follow up period was 4.1 months (0.1-40.7 months). The median OS was found to be 4.73 months (0.4-41.8 months). Multivariate analysis demonstrated that RPA class was a significant predictor of death (HR = 2.263, $P = 0.038$). The number of lesions, tumor histology, Graded Prognostic Assessment score, prior whole-brain radiation therapy, prior resection, prior chemotherapy, patient age, patient sex, controlled primary tumor, extracranial metastases, and planned treatment volume were not significant predictors of OS.

Perspective

Since the update of the GKS facility, more patients with many brain metastatic lesions can be treated with GKS. Reflecting this trend, in the recent update of the National Comprehensive Cancer Network (NCCN) guidelines of multiple (>3) metastatic lesions (Version 1, 2013), the following footnote was removed: "SRS should only be considered in selected cases (e.g. limited number of lesions)." The authors provided treatment results of multiple (5-15) brain metastases treated with GKS. The results showed that the number of lesions did not predict survival time, and RPA class was the only significant predictor of death. Although whole-brain radiation therapy (WBRT) is evidence based and is an effective treatment modality for multiple brain metastases, many neurosurgeons, even until now, like to defer WBRT due to cognitive dysfunction after WBRT even though SRS can be effective in multiple metastases with a lower chance of cognitive dysfunction. Although this study is a single institution retrospective analysis, the results could serve as important base line data for future prospective clinical trials of multiple brain metastases treated by GKS. Summary written by: Jin Mo Cho MD. Quality of life and treatment outcomes for geriatric patients with Type-II dens fractures.[6]

QUESTION

In elderly patients, does surgical stabilization of Type-II dens fractures improve outcomes when compared with nonsurgical treatment (immobilization)? What is the effect of surgery on functional outcomes and are the risks of operative intervention?

A multi-center prospective study was conducted to evaluate surgical and nonsurgical treatment of Type-II dens fractures in geriatric patients. In total, 159 patients were enrolled. Of these, 101 were treated with surgery (primarily C1-C2 fixation) and 58 were treated conservatively (collar immobilization). All the patients were evaluated at 6 and 12 months. Outcomes utilized included Neck Disability Index (NDI) and Short-Form (SF)-36. Patients were additionally followed for potential morbidity and mortality during the follow-up period.

The current study provides Level II evidence in support of surgical stabilization in patients aged >65 years with Type-II dens fractures. In the 101 patients treated with surgical stabilization, these patients had significantly better outcomes as assessed by both NDI and SF-36 bodily pain scores as compared with the nonsurgical group. At 1 year, the NDI worsened by 14.7 points in the nonsurgical group ($P < 0.05$) as compared with only 5.7 points in the surgical group (P = ns). Importantly, the surgical group had a significantly lower rate of nonunion (5% vs. 14%). In addition, mortality was higher in the nonsurgical group (26%) as compared with those patients treated surgically (14%).

In this prospective, multi-center study, surgical treatment of Type-II dens fracture produces better functional outcomes and better fusion rates. Further, despite the risks of surgical treatment in the elderly population, overall morbidity remains lower than nonsurgical treatment with collar immobilization. The data from this multi-center study provides Level II evidence in favor of

surgical stabilization following Type-II dens fractures in the geriatric population.

Perspective

Type-II dens fractures are a notoriously difficult problem in geriatric patients. Morbidity associated with this pathology is associated with both surgical and nonsurgical treatments. Complications have been found associated with halo-vest and cervical collars in addition to the known risks of surgical stabilization. Geriatric patients may also have co-morbid conditions that pose a risk for morbidity as well as fracture nonunion.

This paper provides excellent Level II evidence in favor of open surgical stabilization following injury, even in this difficult patient population. Despite the risks of surgery, immobilization without fixation can be equally morbid and underperforms surgery with regard to fusion rates. Age does not appear to be a contraindication to surgical stabilization of Type-II dens fractures. This report strongly favors surgical treatment, especially in the geriatric population. Summary written by: Zachary A. Smith MD.

QUESTION

Does primary genomic analysis of sporadic meningiomas facilitate classification into molecular subtypes, and is there any association with anatomical location?[1]

Clark *et al.* performed genome-wide genotyping and exome sequencing on 50 non-*NF2* meningiomas, followed by targeted sequencing of candidate genes in an additional 250 samples as well as matched normal DNA. The authors found mutations in *NF2* in 37% of samples, and *TRAF7* mutations in nearly 25% of samples (which were always exclusive from *NF2* mutations). Two additional genes with frequent mutations were *AKT1* and *KLF4*; these mutations almost always coexisted with those seen in *TRAF7*. Finally, 11 tumors (3.7%) had a mutation in *SMO*. Loss of chromosome 22 was seen in nearly half of tumors, and was associated with *NF2* coding mutations. Hierarchical clustering analysis of gene expression data easily separated the major subtypes. Finally, a strong associated was identified between the genetic mutation subgroup and tumor location. Meningiomas with *NF2* mutations were typically located in the hemispheres, posterior fossa, and spinal cord. Those with *TRAF7/KLF4* mutations were more likely found in the lateral skull base, whereas meningiomas with *AKT1* and *SMO* mutations were more likely found along the medial and anterior skull base.

Perspective

This is a landmark study that utilized genome-wide sequencing techniques followed by targeting validation analysis to demonstrate subtypes of non-*NF2* meningiomas. The results from this major study corroborated previous findings with regard to *NF2* mutations and loss of chromosome 22 as a major subset of sporadic meningiomas. More importantly, they demonstrated three new subclasses of meningiomas (*AKT1*, *TRAF7/KLF4*, and *SMO*) that were somewhat less common, and that each subclass was associated with a predilection for a specific anatomical location throughout the intracranial space. This study is a major step toward precision medicine for patients with meningiomas based on phenotypical and molecular characteristics. Summary written by: Gabriel Zada M.D.

QUESTION

Implications of poly (*N*-isoproplyacrylmaide)-g-poly (ethylen glycol) with codissolved brain-derived neurotrophic factor injectable scaffold on motor function recovery rate following cervical dorsolateral funiculotomy in the rat.[2]

Perspective

Treatment of spinal cord injury remains a challenge in the field of trauma neurosurgery. Currently available therapy aims to remove compressive lesions and restore the spine into its appropriate alignment, as well as maintenance of a physiological environment to minimize secondary injury. Development of specific pharmacological therapy for spinal cord injury has been disappointing. One active area of research focuses on the use of various chemical and physical agents to promote axonal growth. This paper looks at the effect of BDNF, which showed encouraging results. However, much is left to be done as experimental models are significantly different from the real world patient injuries. Application of this intervention in other experimental models such as primate models or other injury models will be interesting. Summary written by: Vincent Wang M.D., Ph.D.

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