Clinical Study

Fabrication and testing of a device capable of reducing the incidence of ventricular shunt promoted metastasis

Edward C. Halperin, Thaddeus Samulski, W. Jerry Oakes and Henry S. Friedman

Departments of Radiation Oncology and Pediatrics, Duke University Medical Center, Durham, North Carolina, USA; The Division of Pediatric Neurosurgery, Department of Surgery, University of Alabama at Birmingham, Birmingham, Alabama, USA

Key words: brain neoplasms, medulloblastoma, ventricular shunts

Abstract

Purpose/Objective: Some malignant brain tumors shed cells into the cerebrospinal fluid (CSF). These tumors may implant throughout the neuroaxis via the CSF. With the placement of a ventriculoperitoneal (VP) or ventriculoatrial (VA) shunt, tumor cells free-floating in the CSF may be carried through the shunt to the remainder of the body. Mechanical filtration devices to prevent this are not reliable. We report the development of a new device capable of reducing the incidence of shunt promoted metastasis.

Materials & Methods: The device exposes the draining CSF, as it passes through a baffle system, to a localized high-intensity radiation field adequately shielded from surrounding normal tissue. The prototype consists of geometrically fixed iodine-125 ($^{125}$I) sources. The device accommodates the maximum CSF flow rate of 500 ml/24 hours. Radiation exposure to clonogenic cells occurs as they transit through the baffle system. Since the volume of the prototype device is 14 ml, a tumor cell floating through the device will be exposed to radiation for 40 minutes. Utilizing the human medulloblastoma cell line D425 MED, a limiting dilution clonogenic assay was performed. Suspensions of tumor cells in liquid medium were pumped through the device at the maximum anticipated CSF production rate of 0.35 ml/min. After the cells, with their tissue culture medium, were received from the device, a series of nine 5-fold dilutions were prepared from the suspensions which initially contained $10^6$ tumor cell/ml. Plates were then incubated and growth was demonstrated by visual scoring of colonies of more than 20 cells. Limiting dilution data analysis was performed. Radiation surveys of the fully loaded (approximately 1.8 Ci) $^{125}$I prototype were conducted. A well calibrator was used to measure the activity of the fully loaded device.

Results: When the device was loaded with $^{125}$I seeds providing a dose of 364–479 cGy the probability of clonogenic survival was 0.033. Radiation exposure levels at the exterior surface of the shielded device were in the range of 2–5 mR/hr and thus fell within guidelines for acceptable normal tissue exposure. Attenuation of radiation by the shielding case for the fully loaded device was $10^{-5}$.

Conclusion: The device kills medulloblastoma cells as they are pumped through it. If the risk of metastasis is linearly related to the number of clonogenic cells, then the device would, we infer, reduce the risk of shunt-born metastasis by a factor of 0.033 and merits further investigation.
Fig. 1. The inner fluid chamber of the CSF Irradiator is machined from biocompatible plastic material. The external shield enclosure is fabricated from a cobalt-based alloy, MP-35-N. The ports on the side allow entrance and exit of the CSF and are attached to the subcutaneous shunt tubing.

Introduction

Malignant brain tumors rarely cause death by systemic metastatic spread beyond the central nervous system (CNS). Rather, the principal mechanisms for causation of death and disability are either local infiltration or spread within the neural axis. Some brain tumors shed malignant cells into the surrounding cerebrospinal fluid (CSF). These malignant cells may live for several days in the CSF and implant elsewhere in the CNS. Medulloblastoma, for example, may shed cells and produce tumor implants, carried by the CSF, to the spinal cord or over the convexities of the brain [1–6]. It is commonplace, therefore, to analyze the CSF for the presence of tumor cells, as well as to evaluate, using radiologic techniques, the possibility of tumor implantation along the spinal axis or in the brain.

Among the more common results of the local expansion of brain malignancies is the production of hydrocephalus. The contemporary therapy of tumor-associated hydrocephalus often involves the placement of a shunt. These conduits, usually fabricated of siliconized elastic tubing, are introduced into the lateral ventricle proximal to the point of obstruction [7–8]. The tubing is directed around the point of obstruction into a body cavity capable of absorbing or otherwise disposing of the excess CSF. The most common shunt procedure is the ventriculoperitoneal (VP) shunt, although the cisterna magna (ventriculocisternal shunt), pleural cavity (ventriculopleural shunt), and the heart (ventriculoatrial shunt, VA) may be used for this purpose.

While the development of the VP shunt has been a great service to patients with tumor-induced hydrocephalus, it has resulted in a peculiar form of tumor spread – the shunt-borne metastases. Concurrent with the development of the use of systemic diversionary shunts in patients with brain tumors, reports began to appear concerning the development of metastatic spread of CNS tumors through shunts [9–10]. It would be ideal to have a shunt which would relieve hydrocephalus and not disseminate tumor before definitive surgery, radiotherapy, and/or chemotherapy could be brought to the fore to attempt a cure.

In this paper, we describe the development and testing of a new type of shunt filter. Our device relies on the killing ability of ionizing radiation. Because of the long established nature and widespread acceptance of the concept of the radiation clonogenic assay, the device’s efficacy is testable in vitro. We herein describe experiments to test the efficacy of this filter in vitro utilizing a clonogenic assay.