News
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******Experimental treatments for brain tumors showing promising results.

DALLAS--Pioneering treatment of brain cancer is providing unique alternatives here for patients with tumors otherwise deemed "untreatable."

Dr. Edward A. Neuwelt, assistant professor of neurosurgery and biochemistry at The University of Texas Southwestern Medical School, and a team of medical researchers have developed three separate procedures for the treatment of brain tumors. Each is considered experimental and up to now studies have been mainly designed to evaluate feasibility, yet each is showing evidence of at least some therapeutic value. Neuwelt says the procedures are being approached with "guarded optimism" by the research team, which includes Dr. Eugene Frenkel, professor of hematology/oncology at Southwestern and director of the Cancer Center there; Drs. Jan Diehl, chief of neuroradiology, and Mark Glasberg, assistant professor of neuropathology and neurology, both of Southwestern, and Dr. Stanley Rapoport of the National Institute on Aging in Baltimore, Md.

"We are involved in an organized, concerted tumor program--not just one protocol," says Neuwelt.

The treatments include 1. the temporary disruption of the "blood brain barrier" in order to allow chemotherapy to reach brain tumor sites, 2. the use of immunotherapy using the patient's own white blood cells which are either injected into the tumor cavity itself or into the spinal fluid surrounding the brain, and 3. a method of operating on pineal tumors that reduces the risk of operative mortality from 35 percent to below five percent (a highly effective chemotherapy regimen has also been developed by the team if the pineal tumor remains or recurs following surgery and radiation therapy).

Neuwelt explains that all brain tumors are life threatening, since any increase in brain mass can increase pressure within the skull to the point of causing death. For many of his patients with tumors in the advanced stages, the experimental treatments represent a "last ditch effort"--the alternative is to remain with their families and wait for death to come.

Conventional treatment of brain tumors has been limited to surgery or x-ray therapy. Yet Neuwelt explains that surgery can only be performed if there is a single tumor in the head, and radiation therapy only slows tumor growth and usually cannot kill all of it. Therefore, he says, other forms of treatment, such as chemotherapy and immunotherapy, are very much needed.

Use of chemotherapy in treating brain tumors has met with special problems not encountere in treating other body tumors. It is not uncommon for tumors which develop elsewhere in the body to metastasize, or spread, to the brain. Yet studies have shown that while tumors outside the brain become smaller in response to drug therapy, tumors within the brain continue to grow. Much of the difficulty has been due to inadequate concentrations of chemotherapeutic drugs reaching brain tumor sites. Within the brain, blood vessel cells are packed tightly together forming the so-called "blood brain barrier," and this compact mass of cells separates brain tissue from most substances in the blood. The tiny blood vessels, capillaries, allow the passage of only one red blood cell at a time and blood flow is slow enough that brain tissue can absorb what it needs through the walls of the supplying vessels. But absorption of many substances is hindered by the tightly connected capillary cells, and just those substances of a certain small size can get between these cells.

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At the present time there are very few drugs available that can cross through the barrier and kill tumor cells, says Neuwelt. There are, however, a number of known tumor-fighting drugs that are able to kill tumor cells outside the brain. Neuwelt's technique allows barrier disruption for a short time to allow drug treatment of brain tumor cells. By injecting large doses of mannitol into the carotid artery over a period of 30 seconds, Neuwelt and co-workers have found that the glue-like bond holding capillary cells together can be broken for lengths of time up to a half hour. (Mannitol is a sugar solution used routinely in emergency rooms to reduce brain swelling. It causes the capillary cells to shrink by secreting their fluid to dilute the strong sugar concentration.) All the tight junctions between the capillary cells temporarily open, and this period of barrier disruption allows time for chemotherapy to be infused. Neuwelt and his team have found that the effects are reversible, in that the integrity of the cells is altered only for a few minutes.

The researchers have discovered that infusions of mannitol can increase the amount of chemotherapeutic drugs taken up by the brain 10 to 50 fold or more. "On the basis of our initial clinical studies, carried out 40 times in nine patients, we feel that this procedure is particularly applicable to metastatic brain tumors, and is relatively safe," says Neuwelt. The first infusion was given in September, 1979, and no severe or permanent side effects of the treatment have been seen.

It was Dr. Rapoport of the NIH who established that unless you infuse the mannitol for 30 seconds in certain concentrations, that you could not open the barrier. At 30 seconds he found he had the optimum opening, and Neuwelt has done other studies to establish how quickly the barrier opens and closes. It closes sooner to the molecules of higher molecular weight and size than to the smaller molecules.

Preliminary studies show that temporary blood brain barrier disruption can have future applications for the infusion of antibiotics for brain infections and absesses. Similarly, in collaboration with Drs. John Barringer and Roscoe Brady of the NIH, animal studies are being done to evaluate the possibility of giving enzymes to infants suffering from the genetic neurologic diseases such as Tay Sachs disease in which enzymes are deficient.

It is the blood brain barrier which is also responsible for keeping white blood cells and other elements of the body's immune system from getting into the brain. White blood cells in other parts of the body often can attack and destroy abnormal cells of a tumor, but not so in the brain.

Neuwelt's immunotherapy procedure is being given to patients with primary tumors in the brain--that is, tumors that originate in the brain. The unique thing about primary brain tumors is that the blood brain barrier and the absence of a lymph system keep them from metastasizing to other parts of the body.

The immunotherapy treatment involves having patients come to Dallas' Parkland Memorial Hospital for one to two days to have their own blood drawn. The blood is put into a centrifuge where its components separate by density. White blood cells called lymphocytes are siphoned off, and they are then either injected directly into a surgically-created tumor cavity by way of a small hole drilled in the skull, or the lymphocytes are injected directly into the spinal fluid which bathes the tumor cavity. Treatment is repeated every three weeks.

"It is our hope and the intention of this technique to determine if by placing these tumor-fighting cells in a position where they can reach tumor cells, that they will cause the tumor to shrink," says Neuwelt. "Patients are told that this procedure is entirely experimental, and that we have no solid proof except in test tube studies that this is helpful. But we do have evidence of improvement in a few patients."

The protocol for the immunotherapy, as well as for the other two procedures, limits the patients in the study to those with advanced tumors. To date, the immunotherapy procedure has been performed 90 times in 12 patients, beginning in 1978. Several of these patients appear to have had at least transient benefit from this therapy. With improvement of some of the technical aspects of the therapy, results in recent patients have been gratifying and appear to be more prolonged.

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The third technique aims at removal of pineal tumors, tumors of the brain's pineal gland. Typically these are surrounded by several large, fragile veins deep within the brain, so that surgeons often will not operate on them since the risk of death through hemorrhage is great. The average rate of operative mortality in many large hospitals still ranges from 35 to 70 percent. Over an eight year period Neuwelt and co-workers have reduced that percentage in their patients to less than five percent, with very little in the way of complications or brain damage. Complete surgical removal of these tumors is often but not always possible, says Neuwelt, even with the added element of precision offered by microsurgical techniques (that is, operating while looking through a microscope) and the use of a newly marketed ultra-sonic aspirator recently purchased by Parkland for more accurate tissue removal. "In the few patients in whom all tumor is not surgically removed, and in whom the tumor remains or recurs even with radiation therapy, we have had total resolution of tumor with chemotherapy. The degree of effectiveness of these drugs on pineal tumors is much greater than has been reported previously.

"While we are seeing curative results in some, particularly in pineal tumor patients, we are extremely careful to be almost pessimistic with our patients," Neuwelt says. "The only positive thing we can tell them is that we believe the treatments are fairly safe and they offer hope."

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