CHEMOTHERAPY OF BRAIN TUMORS BY INTRA-ARTERIAL INFUSION

DOGAN M. PERESE, M.D., CARL E. DAY, M.D., AND WILLIAM M. CHARDACK, M.D.

Departments of Neurosurgery and General Surgery, Veterans Administration Hospital, E. J. Meyer Memorial Hospital, Roswell Park Memorial Institute, and University of Buffalo School of Medicine, Buffalo, New York

(Received for publication July 20, 1961)

Several recent reports have dealt with the treatment of malignant tumors of the brain by the isolation-perfusion method. In a small number of patients with primary or metastatic malignancies of the brain, the administration of short-acting chemotherapeutic agents under normal or slightly increased body temperature has been shown to produce palliation for varying periods of time. The main advantage of the isolation-perfusion method is its ability to deliver a relatively large concentration of a drug to the brain without producing much systemic reaction. However, the equipment and preparation necessary for this type of therapy are elaborate, and the system requires the attention and supervision of a team of physicians.

A method of chemotherapy which can be administered by individual physicians without elaborate equipment or a team of auxiliary help, but which provides equal or better therapeutic results than the isolation-perfusion method, forms the basis for this preliminary report.

TECHNIC

The technic, somewhat similar to that suggested by others, was developed by trial and error, and is now carried out as follows:

A No. 16 gauge Tuohy needle is introduced into the common carotid artery under local anesthesia and a carotid arteriogram is performed, using 8 cc. of a 50 per cent solution of sodium diatrizoate (Hypaque). This establishes a baseline from which the results of chemotherapy can be evaluated objectively by means of subsequent visualizations. A polyethylene (or Teflon) catheter about 12 in. long, passing through the lumen of the 16 gauge needle, is introduced into the artery and advanced to a point 1 in. above the bifurcation. The position of the tip of the plastic tube is determined by injecting 1 cc. of sodium diatrizoate through a blunt-tipped No. 20 needle fitted to the end of the catheter. To prevent clotting, the tube is flushed with a solution of heparin in saline every 2 min.

After satisfactory position of the tip of the plastic tube has been established, the outer No. 16 Tuohy needle is withdrawn. The inner tube is held steady to prevent its dislocation. Slight pressure is applied to the opening in the skin for a few minutes after removal of the needle to control the oozing of blood. Reflux of the blood in the plastic tube is prevented by injection of a heparin solution (1 mg. to 1 cc.) into the tube, with the aid of a three-way stopcock connected to the No. 20 needle threaded to the end of the plastic tube.

Frequent irrigations are not necessary, but it is advisable to flush the tube every 8 hrs. to maintain its patency. The plastic tube is anchored to the skin around the puncture hole with adhesive tape to prevent its dislodgement (Fig. 1). Sometimes it may be desirable to keep the patient under some degree of restraint to prevent him from pulling the tube out.

For the vertebral artery, a No. 17 Tuohy needle is inserted, and a proportionally smaller plastic tube is used. Occasionally, it may be necessary to introduce the catheter into the vertebral artery by surgical exploration rather than by the percutaneous approach. We have found it safer to delay chemotherapy for at least 12 hours after the arteriogram.

METHOD

In the cases to be described, an indwelling catheter was placed in the cerebral vessel to be infused. Previously reported attempts to infuse the cerebral vessels were made by injecting the chemotherapeutic agent through a needle. The advantages of the
indwelling-catheter technic are obvious, because this intra-arterial catheter permits the use of fast-acting alkylating agents as well as slow-acting antimetabolites. In this series, the catheter in the cerebral vessel was left in place for as long as 6 weeks without any harmful effect.

The catheter is connected to a rubber tube which runs between the discs of a pump regulating the flow of the fluid coming from the intravenous bottle containing the chemotherapeutic agent. The pump (Fig. 2) costs less than $100, and requires only occasional attention during a 24-hour period. It runs continuously for weeks at a time. Since the discs of the pump are in contact only with the outer wall of the rubber tubing during its "milking" action, the sterility of the entire system is maintained. The rate of infusion can be varied from 1 cc. per min. to 1 cc. per hr. The type of chemotherapeutic agent and the condition of the patient should be considered in choosing the speed of the infusion.

MATERIAL

Intra-arterial-infusion therapy was administered to 12 patients with primary malignant brain tumors who had not responded to conventional methods of therapy.

Nitrogen mustard was chosen in preference to other short-acting alkylating agents because of the availability of an antidote. Six patients received nitrogen mustard at a rate of 5 to 10 mg. administered over a period of 30 min. Simultaneously with the intra-arterial infusion of nitrogen mustard, 100 mg. of sodium thiosulfate were given intravenously for each mg. of nitrogen-mustard solution, to protect the patient from the systemic toxicity of the nitrogen mustard. Sodium thiosulfate was prepared in 10 per cent solution from 1 gm. ampoules produced by the Eli Lilly Company. It was possible to prevent depression of the hematopoietic system by the use of sodium thiosulfate in patients receiving nitrogen mustard daily for 6 days. The administration of nitrogen mustard in doses larger than 5 mg. a day was accompanied by edema of the eyelids, protrusion of the eyeball, discoloration of the skin of the forehead, and edema of the brain, as was demonstrated in 1 case on postmortem examination.

Six other patients with glioma of the brain were given Methotrexate. This antimetabolite, in daily doses of 12 to 14 mg. dissolved in 1200 to 1400 cc. of saline, was administered at a rate of 1 cc./min. The use of citrovorum factor as an antidote was delayed until mild symptoms of toxicity of the drug appeared. This usually occurred after 80 mg. of Methotrexate had been administered within a period of a week. The
use of citrovorum factor simultaneously with Methotrexate would permit the arterial blood carrying the antidote to reach the tumor and protect it from the effect of the drug. Administration of the antidote should not be delayed, however, when fast-acting nitrogen mustard is used. It is not possible to administer slow-acting antimetabolites with the isolation-perfusion technic uninterrupted over a period of several days, and the infusion method presents a definite advantage in this regard. A total dose of 300 mg. of Methotrexate was given over a period of 6 to 7 weeks in three treatments comprising 100 mg. each.

RESULTS

Of the 6 patients with primary malignant brain tumors (glioblastoma multiforme), 2 died within a week after treatment was begun with nitrogen mustard. Their condition before chemotherapy was far advanced and the administration of intracarotid nitrogen mustard may have hastened their demise. One patient, who weighed 62 kg., had received only 15 mg. of intracarotid nitrogen mustard over a period of 3 days when he suddenly went into status epilepticus and expired. Autopsy showed a large necrotic and hemorrhagic glioma in the temporal lobe, causing compression of the brain stem. There was diffuse but moderate edema of the brain. Another patient died from bleeding within the tumor, after one dose of 5 mg. of nitrogen mustard.

The other 4 patients survived the treatment for 3 to 9 months. Since all the patients in this group had had surgical and radiation therapy previously and had varying degrees of neurological deficits preceding chemotherapy, which had occurred within the past 4 weeks, there was some opportunity to assess the results of treatment. One patient with aphasia showed no change after one course of therapy amounting to 30 mg. of nitrogen mustard in 6 days. However, of the 3 remaining patients, 1 showed dramatic improvement of aphasia, and 2 showed improvement of hemiplegia. The improvement lasted for 3 months, with recurrence of the symptoms after this period. A second course of therapy was given to 2 patients, who had remissions of their symptoms lasting up to 4 weeks.

In the group of 6 patients receiving Methotrexate, there were 5 with glioblastoma multiforme and 1 with oligodendroglioma. In the latter case, signs of increased intracranial pressure developed suddenly before intracarotid therapy was started. Methotrexate was administered to this patient, who weighed 72 kg., at a rate of 12 mg. a day in 1200 cc. of saline. On the 5th day of therapy, he became comatose. The pupil of his eye on the side of the parietal-lobe tumor became dilated. There was no improvement in his condition after the administration of 70 mg. of urea solution, although the dilated pupil regressed to its normal size. Six hours before his demise, the pupil on the opposite side became dilated. Apparently, the reduction in the size of the brain was accompanied by a shift of the temporal lobe on the opposite side, with resultant compression of the 3rd nerve. Autopsy showed extensive necrosis and cyst formation within the distribution of the internal carotid artery on the same side of the infusion. The only recognizable mass of tumor amounted to 25 gm., and was located in the posterior thalamus supplied by the branches of the posterior cerebral artery.

A 42-year-old man with glioblastoma multiforme of the temporal lobe was treated because of recurrent hemiplegia. Two months before infusion therapy, this patient had had an infection of the scalp, necessitating removal of the bone flap. He received 100 mg. of Methotrexate through the internal carotid artery and another 100 mg. of the drug through the vertebral artery during a 6-week period. Because of stupor and lack of response, therapy was discontinued. He had shown no depression of the bone marrow, but there were some mild symptoms of toxicity as evidenced by temporary ulceration of his lips. He expired 2 months later. Necropsy revealed diffuse encephalitis and massive necrosis of the tumor.

The remaining 4 patients received the
Methotrexate through the internal carotid artery. Slow but progressive improvement was observed in the neurological deficits of 2 patients, and only subjective improvement in the other 2 patients. In comparison with nitrogen mustard, the recovery of lost functions occurred much later, about 6 to 8 weeks after beginning therapy. All patients showed mild signs of toxicity after receiving 100 mg. within 6 or 7 days, but the symptoms cleared up after 10 to 24 days of abstinence from the drug. Count of the white blood cells did not fall below 2,500, or of the platelets below 100,000. One of the 4 patients returned 3 months later with signs of increased intracranial pressure. Reexploration of the frontal-lobe tumor disclosed a large cyst which had trapped the cerebrospinal fluid because the foramen of Monro had been obstructed by necrotic tissue. Histologically recognizable tumor was found on the wall of the cyst near the caudate nucleus. All 4 patients lived from 6 to 12 months after therapy. One patient with glioma of the temporoparietal lobe has shown recurrence of his hemiplegia after 12 months’ remission. Another patient has been free of symptoms for more than 16 months. As a result of recurrence of their tumors, the other 2 patients expired within 6 months after therapy.

DISCUSSION

The isolation-perfusion technic, in the true sense of the term, is not applicable to the brain. Of the two major vessels (internal carotid and posterior cerebral arteries) supplying each hemisphere, the internal carotid communicates with the external carotid system by way of the ophthalmic artery and minute dural arterioles. The internal carotid contributes to the blood circulating in the anterior and the middle cerebral vessels, which supply two-thirds of the hemisphere, whereas the posterior cerebral artery receives the blood from the basilar tree and supplies the portions of the occipital, temporal, and parietal lobes and the basal ganglia. Under normal conditions, blood from the internal carotid does not enter the posterior cerebral artery, and the regions of the hemisphere supplied by this vessel receive blood coming from the vertebral artery. This entails the necessity of perfusion or infusion of the vertebral arteries.

Isolation-perfusion of the vertebral artery carries a considerable risk, especially when fast-acting alkylating agents are used. The spill-over into the opposite hemisphere and to the pericranium may amount to 20 to 40 per cent of the quantity of blood circulating in the internal carotid vessel. The return flow by way of the internal jugular vein is inadequate, and hence a considerable portion of the arterial blood from the carotid vessels returns to the systemic circulation by way of the perivertebral basal plexus, the external jugular, and other accessory veins. Exposure of the systemic circulation to the toxic effect of the chemotherapeutic agent cannot be avoided in the isolation-perfusion technic when only one artery and one vein are incorporated in the system. Simultaneous isolation of the two major arteries increases the risk and technical difficulties.

The method of indwelling intra-arterial catheter, on the contrary, is a safe procedure. It has been used in more than 30 patients without any serious complications or mortality. Through an indwelling catheter, it is possible to administer alkylating agents as well as antimetabolites, in doses that can be tolerated by the brain and permit adequate protection of the hematopoietic system, as has been demonstrated in our 12 patients. The mortality of intracarotid isolation-perfusion is high, and so is the morbidity. Its use is limited to a few hours and therefore is not applicable to the use of the slow-acting antimetabolites in the therapy of brain tumors. The cost of the isolation-perfusion method for brain tumors is very high and it can be maintained only in centers where financial considerations are of minor importance. In contrast, infusion by way of an indwelling catheter is a simple method, low in cost, and can be administered by one physician and supervised by the nursing staff of any hospital, large or small.
SUMMARY

A simplified method of chemotherapy of brain tumors by infusion of the carotid or vertebral arteries has been presented. It permits the administration of fast-acting alkylating agents as well as of slowly acting antimetabolites. This infusion type of chemotherapy has been compared with the so-called “isolation perfusion” of the carotid system, and it has been pointed out that isolation of the cerebral circulation is not possible when there are other major vessels delivering 20–40 per cent of the blood utilized by the hemisphere of the brain which were not included in the isolation-perfusion system. The infusion of each cerebral artery can be carried out without resorting to elaborate equipment and auxiliary personnel, as demonstrated in our series of 12 patients with malignant primary tumors of the brain. Protection of the systemic circulation from the deleterious effects of the chemotherapeutic agents has been achieved by using an antidote for the alkylating drugs as well as the antimetabolites.

REFERENCES


2. CHARDACK, W. M. Unpublished data.


