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An Organ-Preserving Selective Arterial Chemotherapy Strategy for Head and Neck Cancer

C. W. Kerber, W. H. Wong, S. B. Howell, K. Hanchett, and K. T. Robbins

PURPOSE: Squamous cancer of the upper aerodigestive tract is a disheartening disease. Despite our best efforts, the long-term survival rate remains only 15% to 40%, and surgical cures often decrease the quality of life owing to the loss of swallowing and speech organs. A better understanding of tumor dynamics and the discovery that thiosulfate can neutralize cisplatin led us to develop a treatment plan that combines a rapid superselective high-dose intraarterial delivery of cisplatin (CDDP), simultaneous intravenous infusion of its antagonist, thiosulfate, and radiation therapy.

METHODS: Patients with advanced head and neck squamous cancer were entered into the protocol after a multidisciplinary evaluation that included CT or MR imaging. Forty-two patients constituted the first cohort. After baseline angiography, an arterial acceptance test determined the maximum infusion rate that the tumor's nutrient artery would accept. CDDP was then infused at that rate, usually within 3 to 5 minutes, while the antagonist thiosulfate was given intravenously. In the second cohort of 85 patients with stage 3 or 4 previously untreated and unresectable disease, local radiation was added to the treatment plan. The radiation dose (180–200 cGy/d $\times$ 35) was delivered regionally on the basis of the known radiosensitizing effect of CDDP.

RESULTS: Cohort 1 allowed us to develop the infusion technique and to establish a dose quantity and delivery frequency. When 150 mg/m² was administered weekly for 4 weeks, no severe toxicity was found. In cohort 2, 72 (92%) of the remaining 78 patients had complete disappearance of their tumor. Seventeen severe toxic events were associated with 323 femoral catheterizations. One patient died of pulmonary embolus, precluding follow-up evaluation. Six patients had neurologic sequelae, three with transient and three with permanent strokes.

CONCLUSION: Rapid superselective chemotherapy with CDDP combined with a circulatory systemic antagonist allowed delivery of an antitumoral drug directly into the lesion while protecting the kidneys and bone marrow from the agent's systemic effects. Use of a dose regimen of 150 mg CDDP/m² per week for 4 weeks resulted in the disappearance of a large percentage of advanced squamous cancers.

The prognosis for patients with advanced head and neck cancer treated conventionally (surgery or radiation therapy or both) is poor, with a long-term survival rate of only 15% to 40% (1). In the last decade, clinical trials with adjunct chemotherapy for untreated head and neck cancers have been encourag-

ing, and pilot studies using cisplatin (CDDP) and 5-fluorouracil have shown success rates of 2% to 50% (2, 3). But to date, we have not been able to find any randomized trials that suggest a long-term survival advantage of such therapy.

Selective intraarterial chemotherapy has been tried in the past (4) but has not gained wide acceptance because of the long infusion times required and catheter-related complications. Now, however, numerous authors suggest it is time to reevaluate its potential (5–15). Theoretically, if one were to use selective intraarterial delivery of the agent, a more favorable therapeutic index could be obtained, providing that systemic toxicity were avoided. CDDP should be an ideal agent, as it has a competitive antagonist, thiosulfate (16–23). CDDP could be infused intraarteri-

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ally, while the thiosulfate is infused rapidly and simultaneously by vein during the arterial infusion. As the reaction product of the two is a nontoxic chelate, systemic toxicity could be minimized. Lee and co-workers (5, 6) have reported their excellent preliminary results using this technique for head and neck carcinomas. We began a phase 1 trial using this strategy in 1988 and have modified it since, now including local radiation therapy. What follows is a description of this technique, the complications we encountered, and the results we have obtained.

Methods

Patients with advanced head and neck cancer were entered into the institutional review board–approved protocol after a careful multidisciplinary evaluation, which included physical examination, laboratory testing, and CT or MR imaging. In the first cohort of patients we determined the body's tolerance to rapidly infused high doses of intraarterial CDDP. Forty-two patients (23 with untreated stage 3 or 4 carcinoma, 19 with recurrent stage 3 or 4 carcinoma) received escalating dosages of CDDP delivered (as close to the tumor bed as anatomically possible) by selective intraarterial catheterization. CDDP antagonist, thiosulfate, was infused simultaneously by vein. Dosage regimens of 120 mg/m² given four times at 4-week intervals was gradually increased to 200 mg/m² given four times at weekly intervals.

The final dosage selected was CDDP 150 mg/m², dissolved 1 mg/mL in isotonic saline (usually about 300 mL), and given as rapidly as the feeding artery would accept the bolus (usually 3 to 5 minutes). Simultaneously, we infused thiosulfate, 9 g/m² in 300 mL of water, the infusion timed to last as long as the intraarterial infusion.

The second cohort of 85 patients was treated with concomitant local radiation (180–200 Gy/d $\times$ 35) based on the theory that CDDP is a potent radiation sensitizer (or vice versa). All patients in this cohort had untreated stage 3 or 4 disease.

On the morning of the arterial infusion, the patients ate a normal light breakfast, were hydrated well both orally and intravenously, and underwent baseline percutaneous angiography by a femoral artery entry site. The procedure was performed with local anesthesia at the groin puncture site plus occasional supplemental intravenous fentanyl and midazolam.

Depending on the patient's age, either a 5F (0.065 $\times$ 0.045-inch) polyethylene simple curve or compound curve catheter was used to engage the orifice of the appropriate brachiocephalic vessel. We then introduced a 260-cm exchange guidewire into the common carotid artery, removed the first catheter, and replaced it with a 5F uncurved polyethylene catheter. That second catheter was placed in the distal common carotid artery 2 to 4 cm proximal to the bulb, and biplane angiographic images were obtained. If additional views were needed they were obtained by using a digital technique (Fig 1).

Next, using roadmapping, we gently entered the proximal external carotid artery, leading the catheter with a curved 0.038-inch hydrophilic guidewire. We did not permit either guidewire or catheter to pass beyond to the origin of the occipital, lingual, or facial arteries. Selective external carotid images were then obtained.

Determining the Infusion Strategy

After analyzing the angiographic images and comparing them with the CT or MR images, we attempted to direct the major CDDP dosage into vessels that were most likely to feed the lesion. It was usually impossible to determine the actual blood supply of the tumors by angiographic criteria, because the carcinomas were typically avascular. If the scans showed a

tumor extending across the midline, a bifemoral approach was used and bilateral simultaneous infusion was carried out. If we estimated that, for example, 70% of the tumor volume was on the left side, that side received 70% of the CDDP. Usually, laryngeal carcinomas were treated by infusion of the superior thyroid artery, tongue base lesions by infusion of the lingual artery, and pharyngeal lesions by infusion of the proximal external carotid artery. The lateral angiographic view was the critical determinant of the infusion strategy, supplemented as necessary by more selective injections.

Arterial Acceptance Test

With the catheter in the vessel feeding the tumor, another angiographic series of images was obtained. We termed this series the *arterial acceptance test*. The catheter, positioned in the region of the expected blood supply, was connected to a Medrad MK IV pressure injector. Contrast agent was then delivered at increasing rates until it refluxed slightly into the more proximal vessels during peak systole. Having thus determined the tumor nutrient artery's maximal acceptance rate (Fig 2), we asked the patient to attempt to dislodge the catheter by repeated swallowing. If the large catheter became dislodged from its position, we then directed a microcatheter through the 5F catheter into the desired vessel and repeated the arterial acceptance test. In some patients, because of specific tumor vascularity or ablation of certain arteries from prior surgery, it was necessary to superselectively catheterize several vessels in turn (Fig 3).

CDDP Infusion

Using double gloves and eye protection, we placed syringes preloaded with CDDP into a pressure injector. The nurse assistant began intravenous thiosulfate infusion and, 30 seconds later, the intraarterial CDDP injection was started while we watched the catheter tip position on live fluoroscopy, 1 to 2 seconds of imaging every 10 to 15 seconds.

At the completion of CDDP infusion, a final series of images was obtained by digital subtraction technique to verify that the catheter had not changed position. If a coaxial microcatheter and carrier catheter were used, the dead space between the guiding catheter and microcatheter was perfused with heparinized saline (6000 U heparin/1000 mL of isotonic saline) given at a rate of 10 to 20 drops per minute.

The patient's condition was monitored continually with ECG, blood pressure, oxygen saturation, and clinical examination. A nurse gave the concomitant medications (most important, the thiosulfate) by vein during the arterial infusion.

Results

Cohort 1 (CDDP Dose Escalation)

We began by giving 120 mg/m² at 4-week intervals and gradually increased the dose to 200 mg/m² while decreasing the time interval between treatments to 1 week. At 200 mg/m², systemic toxicity was thought unacceptably high, and 150 mg/m² was decided upon, and all subsequent patients were treated with this dose at weekly intervals.

Response was determined by physical examination, endoscopy if needed, and by comparison CT or MR studies. A complete response was defined as disappearance of all tumor, a partial response as a decrease in tumor size of 50% to 99%, and no response as either a decrease of less than 50% or an increase in size.

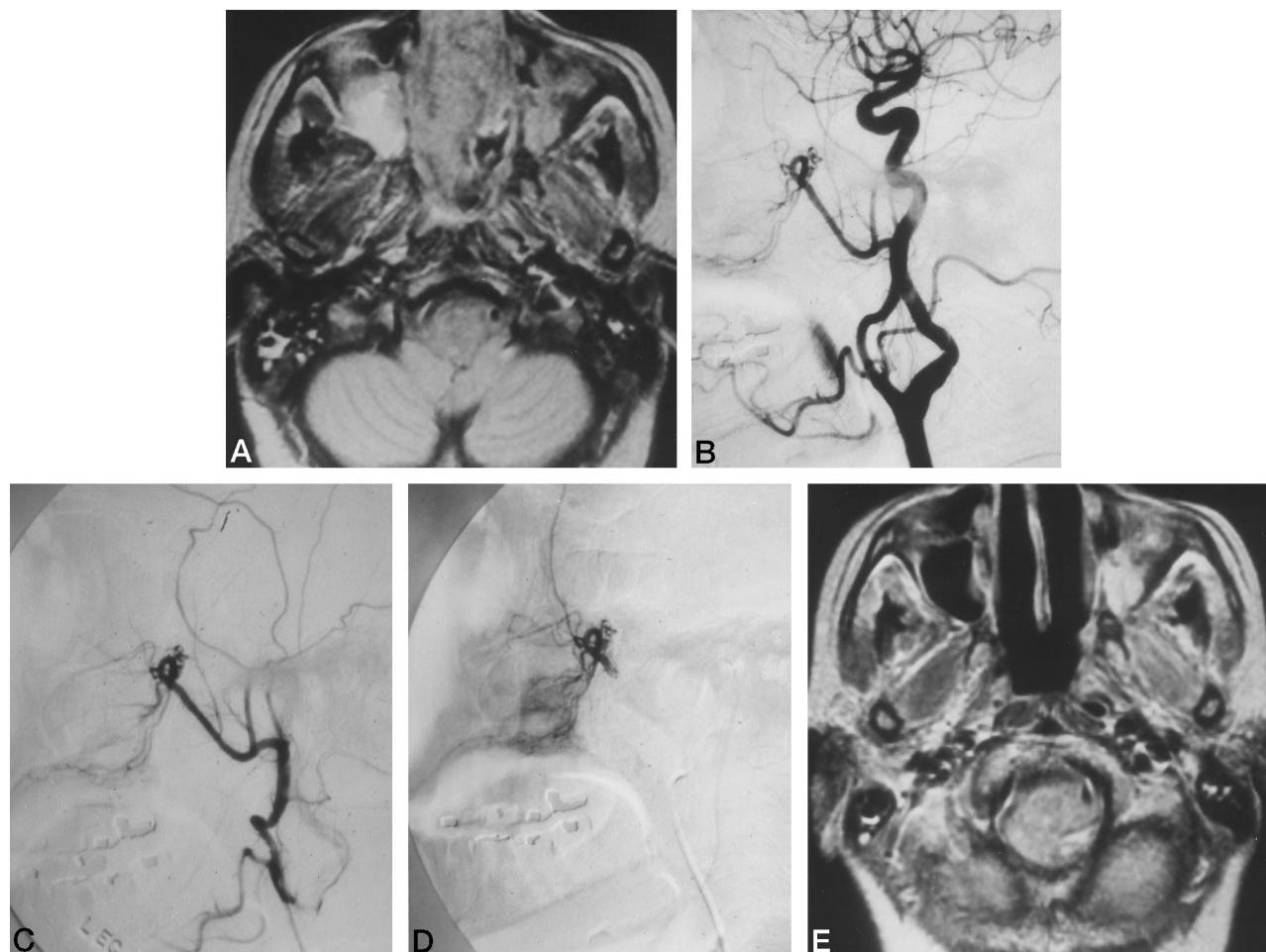


FIG 1. This sequence of images shows the usual workup and follow-up of a patient in the protocol.

A, CT or MRI studies are obtained as part of the initial clinical evaluation to ascertain extent of tumor spread. This axial MR image shows a bulky heterogeneous tumor filling the nasal cavity.

B, Next, we obtained a common carotid angiogram to search for proximal abnormal or aberrant vessels. This view allows us to evaluate the amount and extent of atherosclerosis and the degree of vessel tortuosity, and enables us to determine whether there has been surgical excision of key vessels.

C, A straight 5F catheter is placed within the proximal external carotid artery, and the tumor's blood supply is defined.

D, Having determined that the tumor is nourished by branches of the internal maxillary artery, we position a microcatheter selectively into that vessel. At this point, an *arterial acceptance test* is done. Having determined the artery's maximal acceptance rate, we then infuse CDDP at that rate.

E, Follow-up imaging is performed at varying intervals depending on the protocol details. At 6 months after treatment, no residual tumor is evident in this patient. Eight blind biopsies in the region of the tumor failed to find residual tumor.

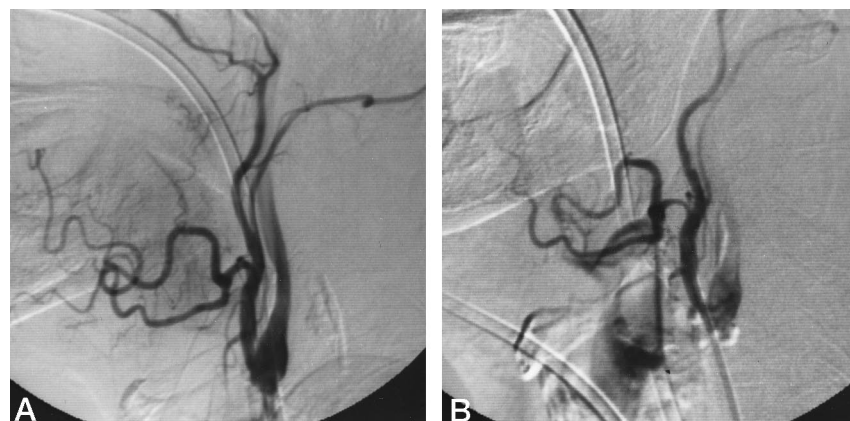


FIG 2. Catheter position as a function of reflux during the arterial acceptance test.

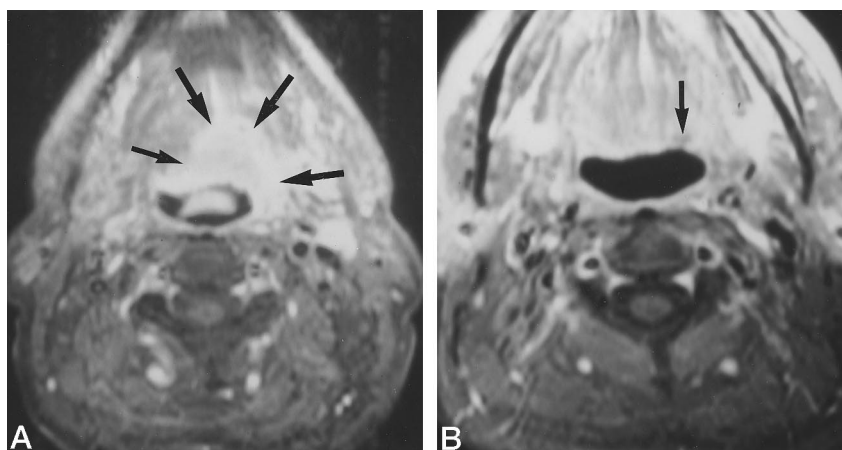
A, The first lateral view arterial acceptance test for this lingual tongue and oropharyngeal carcinoma shows excessive systolic reflux into the internal carotid artery. Injection rate was 3 mL/s.

B, We positioned the catheter 2 cm more distally and repeated the acceptance test. An appropriate and minimal amount of reflux is now visible.

FIG 3. Axial MR images through the base of the tongue.

A, Pretreatment study shows a homogeneously hyperintense lesion along the left side of the tongue base (arrows). Biopsy specimen showed squamous carcinoma. The patient received four sequential CDDP treatments.

B, Two years after the last chemotherapy infusion, only a small hypointense region (arrow) remains. No tumor was seen at clinical examination.



Of the 42 patients, four could not be assessed. One patient refused further therapy after the first treatment, one sustained unrelieved spasm of the artery, and two had abnormal or absent vessels from prior surgery. Thirty-eight evaluable patients remained. Of the 22 who had no prior treatment, nine (41%) had a complete response, 10 (45%) had a partial response, and three (14%) had no response. After chemotherapy, all patients in this cohort had conventional surgery or radiation therapy. In the 16 patients who had previously been treated by surgery or radiation, four (25%) had a complete response, six (38%) had a partial response, and six (38%) had no response.

Toxicity

The majority of patients tolerated CDDP well until it was given at 200 mg/m² separated by only 7-day intervals.

Angiographic Complications and Problems in Cohort 1

Forty-two patients had 140 transfemoral catheterizations. Two infusions failed, one because of toxicity and the other because an atherosclerotic plaque occluded the nutrient artery. Two patients suffered transient arrhythmias that needed no treatment. One patient treated early in the study had transient retinitis with visual disturbance, which resulted from the catheter having been moved by swallowing, causing practically all of one dose to be delivered into the internal carotid artery. This complication led to subsequent modification of our catheterization monitoring procedure. In one patient an 8 × 8-cm groin hematoma developed (no treatment was needed) and in another a 5 × 5-cm region of cutaneous and subcutaneous necrosis was seen after infusion of a superior thyroid artery (no surgical treatment was required and the necrosis healed).

Cohort 2 (CDDP Plus Local Radiation)

Eighty-five patients entered this phase, of whom seven were not evaluable after treatment. All had

untreated unresectable grade 3 or 4 squamous cancer and 62% had N2-3 nodal disease. Of these seven nonevaluable patients, one died of pulmonary embolus during therapy, two died of myocardial infarction after treatment but before reevaluation, two did not complete therapy (one sepsis, one noncompliance), and two did not return.

Seventy-eight patients remained. In this group, the primary tumor showed a complete response in 72 (92%) (Figs 3 and 4), a partial response in five (6%), and no response in one (1%) (Fig 5). The regional nodes showed a complete response in 64 (84%) and a partial response in 11 (14%) of these patients. Thirty of the 52 patients with bulky nodal disease also had neck dissection.

Cohort 2: Toxicity

Among the 84 patients who had a total of 323 arterial treatments, 16 severe toxic events occurred: nine gastrointestinal, seven hematologic. There were six neurologic problems (see below) and one death



FIG 4. Posterolateral view behind right ear of patient who was part of the combined CDDP/radiation cohort.

A, Before treatment, obvious tumor fungates through the skin (arrows). This squamous cancer had originated in the tonsillar fossa and had passed along the skull base to the skin.

B, Three months after treatment, the tumor is no longer visible.

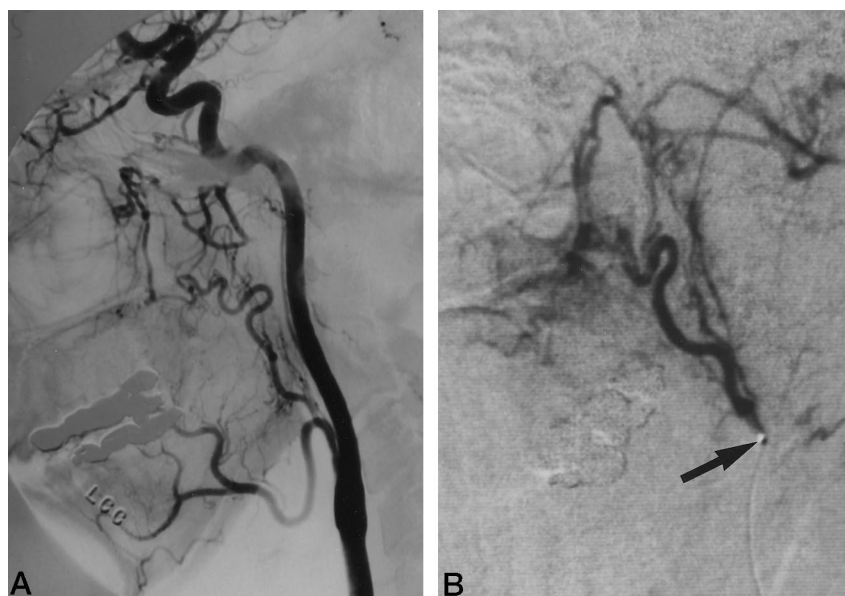


FIG 5. This patient had prior radical neck dissection for a primary tumor in the posterior parotid gland and skull base.

A, Lateral common carotid injection. Surgery had interrupted many of the proximal vessels that would be expected to feed the lesion.

B, Superselective arterial acceptance test through the microcatheter. The tumor was perfused poorly via collaterals. Arrow shows the tip of the microcatheter. Despite our efforts, tumor arterial flow was slow. The patient had a poor clinical response.

secondary to a pulmonary embolus (mentioned previously).

Cohort 2: Angiographic Complications and Problems

During the 323 infusions, only three patients could not be treated: two had atherosclerosis preventing superselective catheterization, and one had hypotension. Six had a postinfusion decrease in neurologic function, resulting in three transient and three permanent strokes.

Discussion

Theory

The arterial advantage of delivering chemotherapeutic agents can be expressed by the equation

$$R_t = 1 + \frac{\text{Plasma clearance of drug}}{\text{Tumor plasma flow}}$$

where R_t is the relative advantage of arterial infusion (24). Thus, better (or more effective) clearance of the agent from the plasma is advantageous, as is decreasing the flow rates of blood through the tumor.

We can increase the plasma clearance by delivering a large and concentrated dose. In this study, the tumor was exposed to a concentration of CDDP some 250 times that achievable by an intravenous dose (Howell S, personal communication). We can increase the R_t by decreasing tumor plasma flow. The arterial acceptance test allows us to do this without resorting to balloon occlusion of the feeding vessel. Simply by increasing infusion rates to the point of reflux into adjacent vessels we stop ingress of all blood (and thus plasma) during the injection of CDDP. Completely filling the artery with the CDDP also prevents the liquid CDDP from streaming into focal areas, as has been found by others (25–28). The

blood's slipstreams remain coherent, and, unless mixing is complete, a stream may pass into a distal vascular bed more selectively than the therapist would wish. Finally, by preventing infusion of circulating blood, we prevent neutralization of the CDDP by the thiosulfate before the CDDP reaches the tumor.

Practical Matters

Aside from the usual attention to catheter hygiene, there are other areas of concern for the angiographic therapist. We have found that a common carotid artery lateral view angiogram best allowed us to develop an accurate and complete map of the extracranial circulation. This set of images was then compared with the axial CT scan and multiplanar MR images. Knowledge of the vascular territories was an aid in treatment. Generally, though, the superior thyroid artery was infused for laryngeal tumors, the lingual artery for tongue base lesions, and the entire external carotid system for posterior pharynx and nasopharynx tumors. If the tumors extended across the midline, bilateral simultaneous injections were carried out, with the majority of the CDDP going to the side containing the largest tumor, in proportion to relative tumoral volume.

The *arterial acceptance test* gives the angiographer a rapid and reliable indication of how fast to infuse the CDDP. Using the same infusion equipment that delivers the CDDP, the angiographer injects a nonionic contrast agent (150 to 180 mg/mL) into the artery supplying the tumor. If no reflux into adjacent vessels is seen during peak systole, the angiogram is repeated at a higher injection rate until this slight reflux is visible. With practice, the angiographer becomes able to judge flow rates with some accuracy, and it is rare to need more than two test runs. When the optimal rate is found, the contrast agent syringe is removed, and the syringe containing the premixed CDDP is connected to the injector and catheter.

We found that most external carotid systems accepted 3 to 4 mL/s through a 5F catheter. Injection through microcatheters was at rates of 1.0 to 1.8 mL/s, higher than that stated permissible by the catheter's manufacturers.

A second critical part of this strategy is that the CDDP's antagonist, thiosulfate, is infused and is circulating through the veins during the intraarterial treatment. Thus, after the first pass of CDDP through the tumoral bed, when it has its primary anticancer opportunity (16), it chelates with the thiosulfate. The reaction product is nontoxic and is excreted by the kidneys (16, 18). To enhance renal excretion, we infuse large amounts of isotonic saline and give osmotic diuretics.

Infusion of a chemotherapeutic agent into flowing blood poses three problems for the angiographer. Poor mixing of the chemotherapeutic agent into a flowing bloodstream has been recognized by numerous authors (25–28). The blood's slipstreams remain coherent, and unless infusion is appropriate to the vessel's runoff, the agent may pass to unwanted areas entirely. Second, the infusion must be as rapid as possible. Third, there is circulating neutralizing agent in the vascular tree, which should be prevented from entering the tumor's feeding artery during treatment. We found that all three problems were solved by finding the vessel's maximal acceptance rate. At this maximal acceptance rate, the tumor's entire arterial volume is taken up by agent, the thiosulfate is completely excluded from the vessel during the infusion, and there is no possibility of the agent passing into an inappropriate single slipstream.

The results in cohort 1 showed that it was possible to infuse a large dose (150 mg/m^2) in minutes and at weekly intervals. No insurmountable technical problems occurred, even with weekly catheterizations (14, 29).

It is not known whether CDDP potentiates radiation or vice versa, but in either case, combining this infusion strategy with radiation treatment was effective (14, 29, 30). In cohort 2, a complete response rate of 92% speaks well for the theory underlying this treatment plan. Although long-term analysis will be the final judge, it is gratifying to see these patients, who often were in pain, stop asking for narcotics within days after the first treatment.

Conclusion

Rapid superselective chemotherapy with CDDP combined with simultaneous infusion of its antagonist, thiosulfate, allowed delivery of the antitumoral agent directly into the lesion while protecting the kidneys and bone marrow from systemic effects. Perhaps the most important outcome of this strategy is the preservation of the patient's quality of life: there is no loss of larynx, tongue, or jaw, and the patient can continue to speak and eat without pain.

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