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Index terms:
Chemotherapy
Chemotherapy, complications
Head and neck neoplasms, 262.373, 27.373, 997.33
Hyperthermia

Radiology 2000; 214:688–692

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Unresectable Primary and Recurrent Head and Neck Tumors: Effect of Hyperthermia and Carboplatin—Preliminary Experience[1]

PURPOSE: To perform a single-arm study to determine the effectiveness of and potential toxic reactions to local hyperthermia and systemic carboplatin (*cis*–diammine–1,1–cyclobutane dicarboxylate platinum II) for the treatment of advanced or recurrent squamous cell carcinomas of the head and neck.

MATERIALS AND METHODS: Eight patients with squamous cell carcinoma of the head and neck and stage IV disease (N2 or N3 neck adenopathy) or recurrent local-regional disease and who were previously and definitively treated were included in the study. Thermochemotherapy was administered every 4 weeks. Recorded end points were tumor response, duration of response, incidence of distant metastases, survival, cause of death, and toxic reactions.

RESULTS: One patient had a complete response to therapy, and two had a partial response. Five patients had no response or developed progressive disease during therapy. Six patients died after 4–13 months of progressive disease. Two long-term survivors received radiation therapy; one also underwent surgical resection for residual neck disease. Each thermochemotherapeutic session was well tolerated, with minimal discomfort. Toxic reactions included hypotension, vomiting, hyponatremia, anemia, thrombocytopenia, and infection at the site of administration. There were no life-threatening toxic reactions.

CONCLUSION: The combined use of hyperthermia and carboplatin shows potential in the management of unresectable head and neck tumors and is safe and well tolerated. Further studies on thermochemotherapy are warranted to assess its potential.

Modern units for the induction of superficial hyperthermia are able to produce a selective heating pattern between the tumor and the adjacent normal tissue. Tumor response to hyperthermia alone is transitory, whereas permanent control can be achieved in over 75% of patients when hyperthermia is combined with radiation therapy (1). In the treatment of superficial nodal metastases in the neck, this combination can improve the rates of complete response from 46%, with multiple daily fractionation radiation therapy alone, to 85%, with the addition of heat in a combined schedule (2). In a randomized trial (3), the relative effectiveness of hyperthermia alone, radiation therapy alone, and hyperthermia and radiation therapy was tested by use of spontaneous malignancies in pet animals. Hyperthermia was inferior to the other two treatments and had lower response rates. A randomized study of radiation therapy with hyperthermia versus radiation therapy alone for the treatment of large neck nodes in head and neck cancer revealed superior complete response rates with hyperthermia (82.3% vs 36.8%) (4).

The combined use of hyperthermia and drugs, or thermochemotherapy, has been tested in several cellular and animal systems; it demonstrates an enhancement of the cytotoxic rate over that of hyperthermia alone (5–8). The additive cytotoxicity of the platinum

TABLE 1
Patient Characteristics

Patient No./ Sex/Age (y)	Diagnosis	Prior Radiation Therapy	Prior Surgery
1/F/65	Recurrent SCC of the supraglottis, original stage T4N2b, now with unresectable lymph node on the right side of the neck	Yes	Yes
2/F/65	Recurrent SCC of the nasopharynx, original stage T3N2b, now with recurrent tumor extending to the base of the left side of the neck	Yes	No
3/F/70	SCC of the oropharynx, stage T4N2c, with unresectable lymph node on the left side of the neck	No	No
4/F/73	Recurrent SCC of the supraglottis, original stage T3N2c, now with unresectable lymph node on the left side of the neck	Yes	Yes
5/M/59	Recurrent SCC of the oropharynx, original stage T4N1, now with unresectable lymph node on the right side of the neck	Yes	No
6/M/61	SCC of the oropharynx, stage T2N3, with unresectable lymph node on the left side of the neck	No	No
7/M/65	SCC of the oropharynx, stage T3N3, with unresectable lymph node on the left side of the neck	No	No
8/M/52	Recurrent SCC of the oral cavity, original stage T1N0, now with unresectable mass in the left oral cavity	Yes	Yes

Note.—SCC = squamous cell carcinoma.

coordination complex cisplatin (*cis*–diamminedichloroplatinum II) over that of hyperthermia alone shows a direct dependence on a cellular temperature between 37°C and 45°C in both in vitro (6) and in vivo (7) systems.

Our experience with cisplatin and hyperthermia demonstrated that the combination could be delivered safely, with some activity, in a single-arm trial, although we know that hyperthermia alone can produce a transient response (9). However, cisplatin is difficult to deliver logistically, and there was concern about potential nonhematologic toxic reactions. In the past, vigorous hydration and antiemetic therapy were necessary, which occasionally necessitated extended hospitalization of the patient. Potential mucositis, neurotoxic reactions, and nephrotoxic reactions can also limit the number of cycles delivered (9).

Recently, there have been reports of the hyperthermic enhancement of cytotoxicity with carboplatin (*cis*–diammine–1,1–cyclobutane dicarboxylate platinum II) in human leukemic and adenocarcinomatous cell lines (10,11). In addition, the use of carboplatin at doses of 300–400 mg/m^2 delivered over 20 minutes requires no hydration before or after administration. With this information, in 1989 we began a protocol to examine the effectiveness of and potential toxic reactions to the simultaneous use of systemic carboplatin and local hyperthermia in the treatment of advanced head and neck cancer.

MATERIALS AND METHODS

From July 1990 to January 1993, eight patients (four men and four women; age range, 52–73 years; mean age, 63.75 years) who had histopathologically confirmed squamous cell carcinoma of the head and neck with stage IV disease (N2 or N3 neck adenopathy) (12) or with recurrent local-regional disease and who received previous definitive treatment were included in the study. Patients were selected if they had unresectable nodal disease, as defined by a head and neck surgeon (D.M.R.). Patients could not have distant metastases, metastases to the head and neck, or uncontrolled second primary malignancy. Patients could not have undergone previous chemotherapy. Patient characteristics are summarized in Table 1. Triple endoscopy was performed (by D.M.R.) in all previously untreated primary tumors. All patients were ambulatory and were able to care for themselves at the time of entry into the study.

Informed consent was obtained from all patients after an explanation was given of the objectives, procedures, and potential toxic reactions. The protocol, approved by our institutional review board, was offered to eight eligible patients, and all requested to participate. Three patients who had not undergone prior radiation therapy or surgery were included in the study. We exp lained to these patients that although thermochemotherapy was experimental, induction chemotherapy followed by definitive radiation therapy and/or surgery is commonly used to treat patients with advanced head and neck cancers to improve outcome (13). It was also explained that, regardless of the results of thermochemotherapy, definitive radiation therapy with or without surgery would be necessary.

Patients who received no prior therapy received carboplatin 400 mg/m^2 by means of intravenous infusion administered over 20 minutes during steady-state hyperthermia. Patients who received prior radiation therapy received carboplatin 300 mg/m^2 by means of intravenous infusion administered over 20 minutes during steady-state hyperthermia. Hyperthermia was induced only in the neck nodes. Thermochemotherapy was administered every 4 weeks. No adjustments in the dose of carboplatin had to be made because of myelosuppression, although guidelines for dose modification were specified in the protocol.

The materials used for the induction of hyperthermia were as follows: 17-gauge close-ended Teflon thermochemotherapeutic catheters (Deseret Pharmaceutical; Salt Lake City, Utah) were placed under local anesthesia to monitor the temperature. The thermistors (for tumor heating) used were high-resistance lead Bowman-type, mapped at fixed intervals, or multisensor fiberoptic thermistors; all were accurate to 0.1 cm of National Bureau of Standards traceability. On the basis of the size of the neck adenopathy at the time of treatment, the surface applicators used were model BSD-300, BSD-500, or BSD-1000 (BSD Medical, Salt Lake City, Utah) or more-advanced microprocessor-controlled hyperthermic systems. Constant surface and tumor-volume temperatures were controlled by use of deionized water, which circulated in polyethylene bags.

Thermometric data were spatially mapped along a minimum of two catheters that were interstitially placed into the tumor site and along a third catheter placed on the surface of the skin (14). A complete set of spatial temperature data was collected at a minimum of 7-minute intervals after the initiation of treatment, with constant supervision by physicists, nurses, and physicians throughout the treatment to make adjustments on the basis of temperature measurements or complaints of pain from the patient. The surface applicators applied heat to achieve a minimum temperature of 42°C in the monitored tumor volume for 30 minutes. Carboplatin was infused over 20 minutes during the 30-minute steady-state heating period.

TABLE 2
Response and Outcome

Patient No.	Site of Hyperthermia	No. of Treatments	Clinical Response	Radiographic Response	Patient Outcome
1	Right side of neck	2	NA	Progressive disease	Progressive disease, died at 8 mo
2	Right side of neck	2	NA	No change	Progressive disease, died at 13 mo
3	Right side of neck	3	Partial response	No change	Progressive disease, died at 7 mo
4	Left side of neck	2	Progressive disease	NA	Progressive disease, died at 5 mo
5	Right side of neck	3	NA	Progressive disease	Progressive disease, died at 8 mo
6	Left side of neck	3	Partial response	Partial response	Received radiation therapy, underwent surgery for residual disease, no evidence of disease at 6.5 y
7	Left side of neck	3	Complete response	Partial response	Received radiation therapy, no evidence of disease at 35 mo
8	Left cheek	1	NA	Progressive disease	Progressive disease, died at 4 mo

Note.—NA = data not available.

The minimal criteria for evaluation were a temperature of 41°C or higher in the tumor that was maintained for at least 30 minutes and the delivery of a total dose of carboplatin of at least 300 or 400 mg/m^2 for at least two treatments. All local and systemic toxic reactions were recorded by use of the toxicity criteria of the Southwest Oncology Group (15). All late toxic reactions were noted at follow-up. Other end points recorded were tumor response, duration of complete response, incidence of distant metastases, survival, disease-free survival, and cause of death.

Response was based on neck adenopathy and on shrinkage or stability in size of the primary tumor by use of the following objective response criteria (16): Complete response was a complete disappearance of measurable and palpable tumor, partial response was tumor shrinkage by more than 50%, progressive disease was growth of tumor by more than 25%, and no change was tumor regression of 50% or less or tumor growth of 20% or less. Subjective responses were also noted, when appropriate. The duration of the response was defined as the time from achievement of a complete response to recurrence. Survival was defined as the interval between the institution of thermochemotherapy and death.

Diagrams of the primary and neck adenopathy were made with volumetric measurements that were recorded clinically and radiographically. Tumor volumes were calculated from a computed tomographic (CT) image in the following manner. Volumes were estimated by calculating the area the tumor occupied in each section of the CT image and by multiplying the area by the thickness of each section. All volumes were then summated to obtain an estimate of the total volume of the tumor.

The areas that the tumor occupied on each section were calculated as follows. With the help of the radiology staff, tumors were outlined (by P.C.) as accurately as possible in each section of the CT image. Each outline was then traced onto individual self-stick removable notes. Centimeter-scale markers in each section were copied and traced, as well. All self-stick removable notes were organized and copied onto clear plastic transparencies. The transparencies were then magnified to twice their actual size by use of an overhead projector and were projected onto standard graph paper with 1-mm markings that had been affixed to a wall. The scales from the CT images, which were copied onto the transparencies, were used as guidelines. The transparencies were enlarged until the CT scale marker was large enough to occupy 2 cm on the graph paper. This gave a magnification of 2:1.

The number of 5 × 5-mm boxes that each section of tumor occupied were counted and added to obtain the area. When the tumor occupied half a box or less, half a box was counted. When the tumor occupied more than half a box, one box was counted. Once all of the areas were calculated, they were multiplied by 5 mm (the thickness used in the CT sections) to obtain the volume of each tumor section. The volumes were then summated to obtain the total volume of the tumor.

We believed this method was the most accurate manual method available for the calculation of tumor volumes from CT images. (We do not recommend the use of this method by everyone because it is extremely tedious and time-consuming. Now, many CT scanners are able to calculate tumor volumes with spiral CT volume histogram software after outlining the volume of interest [17]. At the time our CT images were obtained, such technology was not available.)

When CT images were unavailable, tumors volumes or areas were estimated from clinical measurements. This was the case for two of the patients. The use of clinical measurements introduced certain assumptions that led to inaccuracies in the determination of the true volume of the tumor (see Discussion) (18,19).

RESULTS

All patients had squamous cell carcinoma of the head and neck (Table 1). Five patients had received previous radiation therapy. Of these, three also underwent prior surgery. Three patients had received no prior therapy.

Responses and outcomes are summarized in Table 2. Four patients were able to complete three sessions of thermochemotherapy, three patients completed two sessions, and one patient completed one session. This patient developed progressive disease and refused further therapy. In each session, all patients received the appropriate dose of carboplatin, as dictated by protocol. In each session, therapeutic temperatures were achieved in all patients.

Three patients responded to therapy. Patient 7 had a complete response to thermochemotherapy. He received radiation therapy for consolidation. He did not have evidence of disease at 35 months after therapy. He was then lost to follow-up. Patient 6 had a partial response to therapy. He went on to receive definitive radiation therapy and underwent surgical resection for residual disease. At 6½ years after therapy, he did not have evidence of disease. Patient 3 met the clinical criteria

TABLE 3
Summary of Toxic Reactions

Patient No.	Total Toxicity Score*	Toxic Reactions†
1	0	None
2	3	Hypotension (1), vomiting (1), hyponatremia (1)
3	4	Thrombocytopenia (3), anemia (1)
4	4	Anemia (2), site infection (2)
5	0	None
6	0	None
7	1	Anemia (1)
8	0	None

* Score is based on the criteria of the Southwest Oncology Group (15).
† Numbers in parentheses are scores.

for a partial response, but she did not meet the radiographic criteria. This patient received definitive radiation therapy at an outside institution. She later developed progressive disease and died 7 months after therapy. The other five patients either had no response to therapy or developed progressive disease during therapy. They all eventually died of metastatic disease and had a mean survival of 7.6 months.

Each thermochemotherapeutic session was well tolerated by the patients, with minimal discomfort. Toxic reactions included hypotension, vomiting, hyponatremia, anemia, thrombocytopenia, and infection at the site of administration (Table 3). Four patients experienced no toxic reactions. Patient 2 experienced hypotension, which temporarily delayed therapy. Her minimum blood pressure was 80/50 mm Hg. The most severe toxic reaction was a recurrent bacterial infection at the site of heat administration and catheter placement. The infection delayed the second administration of thermochemotherapy by 3 months. There were no other delays in thermochemotherapy as the result of toxic reactions. There were no life-threatening toxic reactions.

DISCUSSION

Unresectable nodal recurrence in head and neck cancer poses a clinically important problem, especially when the neck has already been treated with maximum doses of radiation. Uncontrolled local disease may result in substantial morbidity and poor quality of life. Potential problems, such as pain, neck edema, ulceration, infection, airway obstruction, dysphagia, and alterations in voice, may result.

The survival rate for recurrence in the neck is low. Survival rates as high as 50% are possible with surgery only if the tumor is resectable and the primary tumor has been controlled (20). When the neck recurrence is in an area where resection and further radiation therapy are not possible, very few options are left for the patient. The response rates to chemotherapy alone are variable and range from 8% to as high as 50% among selected patients (21). The use of hyperthermia with chemotherapy may enhance tumor regression. In the patient with unresectable nodal recurrence who has been previously treated with radiation therapy, the use of hyperthermia with concurrent chemotherapy may be an option.

Potential problems with the use of thermochemotherapy for recurrences of cancer in the head and neck should be addressed in future studies. The optimal frequency of thermochemotherapy is not known. We administered thermochemotherapy on a monthly schedule. Because treatment was well tolerated, it may be possible to increase the frequency of application to perhaps every 2 weeks or less to improve the response. Cisplatin can be safely delivered twice a month for head and neck cancer (22). Hyperthermia should not be used more than once or twice a week because of the development of heat-shock proteins and thermotolerance (21).

At the time of this study, cisplatin was difficult to deliver logistically, and there was concern about potential nonhematologic toxic reactions. In the past, vigorous hydration and antiemetic therapy were necessary and occasionally necessitated extended hospitalization of the patient. Nowadays, this is not the case. Cisplatin, when combined with heat, may perfuse tumors more readily than does carboplatin (23). In future studies, cisplatin might be used instead of carboplatin in thermochemotherapy. Doses of cisplatin may be adjusted to reduce its toxicity.

The three patients who responded to therapy had no previous history of surgery or radiation therapy. Perhaps neck dissection and/or radiation therapy alters the vasculature and sufficiently reduces the perfusion of chemotherapeutic agents so that response is limited. Although the patients who had been treated with radiation therapy and/or surgery did not benefit from thermochemotherapy in our study, perhaps an alteration of the doses and frequencies of therapy may overcome this lack of perfusion to allow for a response. These issues need to be addressed so that we may identify a group of patients that could potentially benefit from thermochemotherapy.

We also examined the differences in tumor response, as determined with clinical and radiologic measurements. There appeared to be a marked discrepancy between the two measurements in our study. Specifically, patients 3 and 6 did not achieve a partial response when tumor volume was measured radiographically, but they did achieve a partial response when tumor volume was measured clinically. It has been estimated that human error in tumor measurement ranges from 5% to 10% (24). Even when radiologic studies are used to determine response, there can be marked variability (17). We reemphasize that more consistent methods for the determination of response should be implemented, especially in clinical trials, where accurate assessment of response is crucial.

Systemic carboplatin delivered with the local application of heat for the treatment of unresectable squamous cell carcinoma tumors of the head and neck is safe and well tolerated. Another study in which hyperthermia, cisplatin, and 5–fluorouracil were used showed similar results (25). Although we were not able to assess the effect of thermochemotherapy on survival, thermochemotherapy may have potential for sustained palliation of recurrences of head and neck cancer. Further investigation into thermochemotherapy is warranted, even in patients who have undergone previous radiation therapy, to avoid the morbidities associated with uncontrolled local disease in the head and neck.

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