The Role of Intratumoral Therapy With Cisplatin/Epinephrine Injectable Gel in the Management of Advanced Squamous Cell Carcinoma of the Head and Neck

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Objective: To determine the safety and efficacy of targeted antitumor therapy with cisplatin/epinephrine injectable gel in patients with advanced squamous cell carcinoma of the head and neck.

Design: Two prospective, double-blind, placebo-controlled phase III trials of identical design. Crossover from blinded to open-label phase was permitted for patients with disease progression.

Setting: Tertiary referral centers in North America and Europe.

Patients: One hundred seventy-nine intensively pretreated patients with recurrent or refractory squamous cell carcinoma of the head and neck.

Intervention: Cisplatin/epinephrine injectable or placebo gel was administered by direct intratumoral injection; up to 6 weekly treatments. Dose was 0.25 mL of active or placebo gel per cubic centimeter of tumor up to 10 mL total. Patient benefit after local tumor control of the most symptomatic tumor was assessed by patients and physicians using the Treatment Goals Questionnaire.

Main Outcome Measures: Local tumor response and patient benefit attributable to improvements in tumor-related symptoms.

Results: Combined results for the 178 patients with evaluable data in the 2 trials confirmed objective tumor responses in 35 (29%) of 119 patients, including 23 (19%) complete responses achieved with cisplatin/epinephrine gel, vs 1 (2%) of 59 for placebo (P<.001). Tumor response and patient benefit were significantly correlated (P=.006): 47% (17/36) of patients with target tumor responses achieved a rigorously defined benefit based on a prospectively selected treatment goal vs 15% (22/142) of nonresponders.

Conclusion: Cisplatin/epinephrine injectable gel reduces tumor burden, ameliorates tumor symptoms, and provides a new therapeutic option for treating patients with squamous cell carcinoma of the head and neck.


HEAD AND NECK squamous cell carcinoma (HNSCC) is diagnosed in about 40000 Americans per year and more than 600000 persons worldwide.1-3 Most (70%) patients with HNSCC present with locally or regionally advanced disease, nodal metastases, invasion of local structures, and/or distant metastases. Despite aggressive standard therapy, approximately 60% of patients have recurrences.4

Recurrent local tumors can be symptomatic, impair function, and curtail normal activity. In addition, the physical effects of treatment (ie, morbidity associated with surgery, radiotherapy, or chemotherapy) further lower quality of life in patients with advanced HNSCC.5 Therapeutic options for advanced HNSCC are limited. These patients generally have undergone extensive surgery, have received near-maximum tolerated doses of radiation, and are often poor candidates for aggressive combination therapy.6 Therefore, for more effective local and regional control of HNSCC and to minimize systemic exposure and toxicity, locally injectable therapies have been investigated.7

Introduced 3 decades ago, cisplatin given intravenously has proved to be a potent cytotoxic agent for the treatment of HNSCC.6,8 Cisplatin plus fluorouracil is one standard regimen for recurrent or metastatic HNSCC, with an overall response rate of 30%, a complete response rate of 5%, and a median survival of 4 to 6 months.8 However, treatment is often poorly tolerated. Nausea
PATIENTS AND METHODS

Between June 15, 1995, and March 22, 2000, 179 adult patients with recurrent or metastatic histologically confirmed HNSCC were enrolled in 2 identical, multicenter, prospective, randomized, double-blind, placebo-controlled trials (one in North America and one in Europe). The primary end point was an objective response of the designated target tumor, ie, the most symptomatic or threatening tumor. Secondary end point was palliation of tumor symptoms rather than survival as an end point because cisplatin/epinephrine is a local therapy and was not expected to extend survival in this patient population. Individual tumors had to be at least 0.3 cm³ and 20 cm³ or less in size and measurable and accessible for direct intratumoral injection. Eligibility criteria included the following: at least 1 previous course of therapy (surgery, radiotherapy, or chemotherapy) for HNSCC, Karnofsky Performance Status score of 40 or more and life expectancy of 6 months or more, and adequate hematologic and renal function (granulocyte count >1000/mm³, platelet count >75 000/mm³, and serum creatinine level <1.5 times the upper limit of the institution’s normal value for the patient’s sex). Patients with the following were excluded: a history of cardiac arrhythmias, New York Heart Association class III or IV cardiac disease, or known hypersensitivity to active agents, bone collagen, or sulfites; patients who had been treated within 28 days with another HNSCC therapy were also excluded. Tumors that posed an immediate risk of hemorrhage, embolization, or uncontrolled local infection at the treatment site were excluded, as were fibrotic lesions. Tumors that directly involved or threatened to invade the carotid artery were excluded by an amendment after initial experience revealed a risk of cardiovascular events in these patients. Before the first treatment, each patient signed an informed consent approved by the institutional review board at each study center.

The investigational agent was cisplatin/epinephrine gel (IntraDose Injectable Gel; Matrix Pharmaceutical Inc, Fremont, Calif). This viscous, aqueous, biocompatible-biodegradable gel contains cisplatin (4 mg/mL) and the vasoconstrictor epinephrine (0.1 mg/mL); purified bovine collagen forms the basis of the gel matrix. In the placebo gel, 0.9% sodium chloride was substituted for the cisplatin and epinephrine. This gel formulation provides site-specific cisplatin at high intratumoral drug concentrations for extended periods (1-3 days). Because active agents (cisplatin and epinephrine) slowly disperse from the gel, the incidence of toxicities typical of intravenously administered cisplatin is low.11

Patients were randomized 2:1 to receive cisplatin/epinephrine gel or placebo gel, respectively, and were stratified by volume of their primary target tumors (stratum 1, tumors 0.5 to <5 cm³; stratum 2, tumors 5 to ≤20 cm³). The trials consisted of a blinded treatment phase with up to 6 weekly treatments in an 8-week period followed by 4 weekly evaluations and monthly evaluations thereafter. If after 3 treatments tumors did not respond or continued to progress, patients were permitted to roll over into the open-label phase and be treated with the active drug. However, the study blind was not broken until 6 months after the last treatment of the last patient enrolled. At the discretion of the physicians, tumors could undergo a second course of therapy of up to 6 weekly treatments in an 8-week period. The dose was 0.25 mL/cm³ tumor, and tumor masses were measured at each study visit, most often by direct physical examination (ultrasonography, computed tomography, and magnetic resonance imaging were also used). Volume was calculated as (length × width × height) × 0.5.

The test agents were administered in an outpatient setting or brief hospital stay. The physician injected the agent directly into the tumor by means of a 22- to 30-gauge needle under direct visual, computed tomographic, or ultrasound guidance, being careful to avoid major blood vessels. Injection technique depended on the shape and size of tumors; the gel could be injected through several entry points or through one entry point by changing the angle of the needle. The technique was to lay down tracks of gel 1 cm apart to ensure complete exposure of tumor tissue to high concentrations of cisplatin.

The primary end point in this study was objective response of the target tumor. Response was based on change in baseline tumor volume sustained for at least 28 days: complete response (CR) was defined as 100% reduction of tumor volume; partial response (PR) as 50% or greater reduction; stable disease as less than 50% reduction or less than 25% increase; and progressive disease as 25% or greater increase.

The second end point was patient benefit, which was assessed with the validated Treatment Goals Questionnaire and Patient Benefit Algorithm developed to evaluate the benefit of treating local disease in patients with HNSCC.17,18 The Treatment Goals Questionnaire was validated by means of a cohort of patients with head and neck cancer and clinicians experienced in treating these patients. From the questionnaire, patients and physicians prospectively selected a treatment goal associated with the target (most symptomatic or threatening) tumor. Patients selected 1 of 8 “palliative” goals (wound care, pain control; ability to see, to hear, or to smell; physical appearance; obstructive symptoms; or mobility). Progress was graded on a 4-point scale; achievement was defined as 1-point or greater improvement sustained for at least 28 days. Physicians selected 1 palliative goal or 1 of 3 “preventive” goals (prevention of invasion, obstruction, or subcutaneous tumor from breaking through the skin); these goals were either achieved, ie, the event was prevented for at least 28 days, or not achieved, ie, the event occurred.

The independent assessments of the patients and physicians were incorporated into an algorithm such that patient benefit was attained if either (1) both agreed the goal was achieved or (2) one said the goal was achieved and the other said there was no change. Patients were scored “no benefit” if either the patient or the physician said that the patient’s status declined.

Additional end points included time to response (from first treatment to onset of response) and duration of response (time from onset to objective evidence of progression). Safety evaluations included conditions at the site of treated tumors, results of physical documentation of local tissue examinations and laboratory evaluations, vital signs, and adverse medical events.

To improve the efficacy of cisplatin chemotherapy, a novel drug system has been developed that achieves high, sustained, tumoral cisplatin concentrations with...
types. Herein, we present the combined results of 2 human malignant tumors of various histologic types. The cisplatin/epinephrine injectable gel, designed for local tumor control and symptom relief in the open-label phase, was excluded from the efficacy analysis (n=178). The cisplatin administered was 20 mg (range, 0.8-184 mg), and the median cumulative dose of cisplatin treatments (29% [14/48]) and in patients who were platinum naive (30% [21/71]).

In addition to the target tumors, which by definition had to be symptomatic or threatening, other tumors were treated. During the blinded period, a total of 227 tumors were treated with cisplatin/epinephrine gel (including 119 target tumors) and 80 with placebo gel (including 59 target tumors); response rates (CR+PR) were 30% (68/227) and 1% (1/80), respectively. Of the potential prognostic factors analyzed in this study, only a high baseline Karnofsky Performance Status score (P=.02), smaller tumors (P=.03), and oral and facial tumors (P=.03) were associated with higher tumor response rates.

PATIENTS

A total of 179 patients were enrolled. One patient whose tumor was penetrated by the needle but had no drug injected because of pain and who received no other treatments was excluded from the efficacy analysis (n=178) but was included in the safety analysis (n=179). The cisplatin/epinephrine gel group (119 patients) and the placebo gel group (59 patients) were well balanced for prognostic characteristics (Table 1), including age, sex, Karnofsky Performance Status score, duration of disease, and exposure to previous anticancer therapy.

Entry criteria stated that patients must have been previously treated with at least 1 course of therapy. In fact, patients enrolled had undergone multiple courses of therapy: 89% of patients had been treated with multiple modalities including surgery, systemic chemotherapy, and radiotherapy, and 89% of the target tumors were in a previously irradiated field. Thirty-four percent (60/178) of patients had undergone systemic chemotherapy after recurrence, and 27% (48/178) of patients had received cisplatin/epinephrine injectable gel because of pain and who received no other treatments was excluded from the efficacy analysis (n=178). The median cumulative dose of cisplatin treatments (29% [14/48]) and in patients who were platinum naive (30% [21/71]).

In addition to the target tumors, which by definition had to be symptomatic or threatening, other tumors were treated. During the blinded period, a total of 227 tumors were treated with cisplatin/epinephrine gel (including 119 target tumors) and 80 with placebo gel (including 59 target tumors); response rates (CR+PR) were 30% (68/227) and 1% (1/80), respectively. Of the potential prognostic factors analyzed in this study, only a high baseline Karnofsky Performance Status score (P=.02), smaller tumors (P=.03), and oral and facial tumors (P=.03) were associated with higher tumor response rates.

Table 1. Patient Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cisplatin/Epinephrine Gel (n = 119)</th>
<th>Placebo Gel (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, median (range)</td>
<td>61 (31-87)</td>
<td>61 (40-84)</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td>95 (80)</td>
<td>47 (80)</td>
</tr>
<tr>
<td>Male</td>
<td>24 (20)</td>
<td>12 (20)</td>
</tr>
<tr>
<td>Weight, kg, median (range)</td>
<td>64 (36-107)</td>
<td>63 (34-103)</td>
</tr>
<tr>
<td>Time between cancer diagnosis and first treatment with study drug, mo, median (range)</td>
<td>19 (2-386)</td>
<td>18 (4-236)</td>
</tr>
<tr>
<td>Previous therapy, No. (%)</td>
<td>118 (99)</td>
<td>59 (100)</td>
</tr>
<tr>
<td>Single modality only</td>
<td>10 (8)</td>
<td>9 (15)</td>
</tr>
<tr>
<td>Multiple modalities</td>
<td>108 (91)</td>
<td>50 (85)</td>
</tr>
<tr>
<td>Postrelapse chemotherapy</td>
<td>43 (36)</td>
<td>17 (29)</td>
</tr>
<tr>
<td>Cervical</td>
<td>54 (45)</td>
<td>29 (49)</td>
</tr>
<tr>
<td>Oral</td>
<td>32 (27)</td>
<td>10 (17)</td>
</tr>
<tr>
<td>Facial</td>
<td>19 (16)</td>
<td>13 (22)</td>
</tr>
<tr>
<td>Laryngopharyngeal</td>
<td>7 (6)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Other*</td>
<td>6 (6)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Karnofsky Performance Status score, No. (%)</td>
<td>9 (8)</td>
<td>8 (14)</td>
</tr>
<tr>
<td>Karnofsky Performance Status score</td>
<td>100</td>
<td>80, 90</td>
</tr>
<tr>
<td>Karnofsky Performance Status score</td>
<td>80, 90</td>
<td>67 (56)</td>
</tr>
<tr>
<td>Karnofsky Performance Status score</td>
<td>60, 70</td>
<td>39 (33)</td>
</tr>
<tr>
<td>Karnofsky Performance Status score</td>
<td>40, 50</td>
<td>4 (3)</td>
</tr>
</tbody>
</table>

*Nasopharyngeal, cranial, and chest wall.

minimal systemic exposure. This drug system, cisplatin/epinephrine injectable gel, is designed for direct intratumoral injection and has been used to treat human malignant tumors of various histologic types. Herein, we present the combined results of 2 placebo-controlled phase III trials of identical design conducted to compare the efficacy of cisplatin/epinephrine gel with a placebo gel (without active drug) for local tumor control and symptom relief in advanced HNSCC.

RESULTS

RESPONSE OF TARGET TUMORS

As shown in Table 2, the response rate for the target tumor (CR+PR sustained ≥28 days) was 29% (35/119) for patients in the cisplatin/epinephrine gel group and 2% (1/59) for patients in the placebo gel group, a statistically significant difference (P<.001). Most target tumor responses were CRs (19% CRs and 10% PRs). Smaller tumors tended to have higher response rates than larger tumors: CR+PR for stratum 1 was 37% (23/62) and for stratum 2 was 21% (12/57). Forty-four percent (29/119) of patients in both strata maintained stable disease.

Tumor response generally occurred within 2 to 3 weeks of the first treatment (median time to onset of response was 21 days). The median cumulative dose of cisplatin administered was 20 mg (range, 0.8-184 mg), and for epinephrine, 0.5 mg (range, 0.02-4.6 mg). The median duration of response was 78 days (range, 30-554+ days). At last evaluation, only 2 of the responding tumors had begun to progress. Many of the patients with responses were not able to extend their participation in the study beyond a few months because of systemic disease progression, general physical debilitation, or death.

The response rates for patients who rolled over to the open-label phase were similar to those for patients treated with active drug during the blinded phase: 27% (11/41). Note that, between the time of the first placebo gel treatment in the open-label phase and the first cisplatin/epinephrine gel treatment in the open-label phase, median tumor size had doubled from 5.7 cm³ to 10.8 cm³. Similar response rates were also attained in patients who had undergone previous systemic cisplatin or carboplatin treatments (29% [14/48]) and in patients who were “platinum naive” (30% [21/71]).

In addition to the target tumors, which by definition had to be symptomatic or threatening, other tumors were treated. During the blinded period, a total of 227 tumors were treated with cisplatin/epinephrine gel (including 119 target tumors) and 80 with placebo gel (including 59 target tumors); response rates (CR+PR) were 30% (68/227) and 1% (1/80), respectively.

Of the potential prognostic factors analyzed in this study, only a high baseline Karnofsky Performance Status score (P=.02), smaller tumors (P=.03), and oral and facial tumors (P=.03) were associated with higher tumor response rates.

PATIENT BENEFIT AND ASSOCIATION WITH TUMOR RESPONSE

Patient benefit was evaluated by means of a validated instrument (Treatment Goals Questionnaire) that was based on independent assessments by patients and physicians of the patients’ progress toward prospectively selected treat-
ment goals.18 The goals most frequently selected by the patients were improved pain control, improved wound care, relief of obstructive symptoms, and improved physical appearance. These goals were also frequently chosen by the physicians. Patients treated with cisplatin/epinephrine gel attained a significant benefit compared with patients treated with placebo gel: 27% vs 12%, respectively (P = .05). Finally, objective tumor response was associated with patient benefit as measured by the Treatment Goals Questionnaire (Figure): 47% (17/36) of patients whose target tumors responded to treatment attained a benefit vs 15% (22/142) of patients without tumor responses (P = .006).

Additional benefits that were coincidentally documented on the case report forms but not included in the formal patient benefit assessment included improved swallowing, speech, or psychological state; ability to sleep on treatment side; and less drainage. Such unexpected benefits were noted by 25 patients (21%) treated with cisplatin/epinephrine gel and 4 patients (7%) treated with placebo.

SAFETY

Pain during injection was the most common adverse effect of the treatment procedure: 24% (29/119) of patients treated with cisplatin/epinephrine gel reported immediate (within 15-20 minutes) injection-related pain, as did 17% (10/60) of patients in the placebo group. Pain was severe in 2 patients, requiring hospitalization for intravenous morphine; 1 discontinued therapy. Elevated blood pressure and tachycardia were also observed in less than 5% (8/179) of patients treated with active or placebo gel. One episode of hypertension, associated with pain, responded to intravenous morphine.

Local cytotoxic effects at the treatment site (inflammation, bleeding, erosion, ulceration, necrosis, and eschar) were evaluated at each study visit and were observed in 87.4% (104/119) of target tumors treated with active drug vs 62.7% (37/59) of tumors treated with placebo. Injection therapy results in initial erythema, which is followed in several days by local necrosis and eschar formation. As tumor necrosis proceeds, the diseased tissues are replaced by normal healing and reepithelialization. No specific wound care is required; however, the necrotic tissue and eschar can be topically managed with saline or peroxide wet-to-dry dressings as necessary. In the cisplatin/epinephrine gel-treated patients, adverse effects typically peaked at approximately 2 weeks after the first treatment and resolved during the next 3 to 12 weeks. Wound infection (5.9% [7/119] vs 1.7% [1/59] for placebo) and fistula formation (3.3% [4/119] vs 0% for placebo) were reported. One facial abscess requiring intravenous antibiotics was considered severe. Two pharyngocutaneous fistulas required gastrostomy tubes, with 1 patient withdrawing from

Table 2. Response of Target Tumors* During the Blinded Phase

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cisplatin/Epinephrine Gel</th>
<th>Placebo Gel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No.</td>
<td>62 (Stratum 1†)</td>
<td>57 (Stratum 2†)</td>
</tr>
<tr>
<td>Baseline target tumor volume, cm³</td>
<td>Median 2.0</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Range 0.49-5.0</td>
<td>6.0-20</td>
</tr>
<tr>
<td>Objective tumor response, No. (%)</td>
<td>CR + PR 23 (37)</td>
<td>12 (21)</td>
</tr>
<tr>
<td></td>
<td>CR 16 (26)</td>
<td>7 (12)</td>
</tr>
<tr>
<td></td>
<td>PR 7 (11)</td>
<td>5 (9)</td>
</tr>
<tr>
<td></td>
<td>95% CI for response rate, %</td>
<td>25-50</td>
</tr>
<tr>
<td></td>
<td>P value vs placebo gel</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total No. of treatments to target tumor</td>
<td>Median 4</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Range 1-6</td>
<td>1-6</td>
</tr>
<tr>
<td>Time to onset of response, d</td>
<td>Median 21</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Range 7-162</td>
<td>7-104</td>
</tr>
<tr>
<td>Duration of response, d</td>
<td>Median (30-5168)</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Range (36-554)</td>
<td>(36-554)</td>
</tr>
</tbody>
</table>

*The most symptomatic or threatening tumor. CR indicates complete response; PR, partial response; and CI, confidence interval.
†Stratum 1 tumors, 0.5 to less than 5 cm³; stratum 2 tumors, 5 to less than 20 cm³.

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the study. Bleeding occurred at the injection site in 2 patients and responded to local management. Four patients discontinued the study as a result of blindness, facial pallor, allergic reaction, and anemia requiring transfusion.

There were rare reports of the toxic effects usually observed with systemically administered cisplatin—neurotoxicity, hematologic toxicity, and ototoxicity. Early in the course of the North American study, 4 cases of treatment-related cerebrovascular events occurred (3 in the cisplatin/epinephrine gel group and 1 in the placebo group) either during or shortly after treatment; no additional treatment-related events occurred after protocols were modified to exclude tumors directly invading or in proximity to the carotid artery. Two patients developed dehydration requiring intravenous fluids. During the blinded phase, the incidence rates of treatment-related systemic adverse events occurring in more than 3% of patients in the cisplatin/epinephrine gel group were as follows: vomiting, 7 patients (6%); nausea, 7 (6%); pain, 6 (5%); and headache, 5 (4%).

In these 2 randomized, double-blind, placebo-controlled phase III trials, cisplatin/epinephrine gel was shown to be effective in producing clinically meaningful response and palliative benefit in a group of patients with advanced HNSCC who had few, if any, remaining therapeutic options. Moreover, the strong association between response and patient benefit clearly demonstrated the advantage of treatment over placebo.

In this study population of intensively pretreated patients with HNSCC, the tumor response rate (CR + PR) in the cisplatin/epinephrine gel treatment group was 29% (35/119). In contrast, only 1 patient in the placebo group had a response. Complete responses were nearly twice as frequent as partial responses; this is in contrast to systemic chemotherapy, where a PR is observed 5 times more frequently than a CR.5,6,10,20 Patients enrolled in these trials were in advanced stages of their disease, and in this context, the rapid onset of response (median of 21 days) and response duration (median, 78 days; range, 30-554+ days) were clinically meaningful. Many patients continued in local remission at the time of study withdrawal or start of confounding therapy. Indeed, responses lasted long enough to impact patient wellbeing as reflected in the achievement of patient benefit.

We found several prognostic factors associated with high tumor response rates: smaller tumors; oral and facial lesions; and high Karnofsky Performance Status scores. As with systemic chemotherapy, patients who are markedly symptomatic and less than fully ambulatory have a significantly lower response to therapy and have a shorter expected survival.21 Most important, previous systemic cisplatin or chemotherapy was not a prognostic factor, suggesting that this novel formulation of cisplatin/epinephrine injectable gel is able to intensify dose and exposure time to tumor and thereby overcome resistance frequently observed with systemic cisplatin therapy.

The main goal of treatment in advanced HNSCC is control of local symptoms or prevention of symptomatic deterioration.21 In this trial, the benefits derived from local treatment were measured with a new quality-of-life instrument, the Treatment Goals Questionnaire, for evaluating individualized patient- and physician-selected treatment goals associated with symptomatic tumors.17,18 Independent physician and patient assessments of progress toward their selected goals are combined to produce the dichotomous outcome, “patient benefit” or “no patient benefit.” Such an index provides information not captured in global quality-of-life assessments. Subjects treated with cisplatin/epinephrine gel achieved a higher rate of patient benefit as measured by the validated Treatment Goals Questionnaire than those treated with placebo gel (P = .05). Furthermore, patient benefit was positively associated with target tumor response (P = .01), suggesting that treatment of these symptomatic or threatening tumors has an impact on quality of life that is meaningful to both the patient and the physician. Patients with tumor response were 3 times more likely than nonresponders to benefit from treatment.

The adverse event profile of cisplatin/epinephrine gel differed greatly from that of systemically administered cisplatin. As expected, localization of cisplatin in the gel formulation contributed to fewer systemic adverse effects than intravenous administration of cisplatin. However, predictable local tissue effects, including erosion, ulceration, and necrosis, did occur as a result of the cytotoxic activity of the drug. An unexpected severe adverse event occurred in these studies with cisplatin/epinephrine gel: cerebrovascular events (3 in the active drug group and 1 in the placebo group). All events occurred in larger tumors (10-20 cm³) that were known to impinge on the carotid artery and were most likely caused by vasospasm or inflammation as a result of direct irritation or trauma to the artery or tumor. After the protocols were modified to exclude tumors directly invading or in immediate proximity to the carotid artery, no additional cerebrovascular events related to treatment occurred.

It is of interest to compare the results obtained with this site-specific form of cisplatin with results of standard systemic cisplatin treatment. In a randomized phase III study comparing systemically administered cisplatin and fluorouracil as single agents and in combination for first-line therapy in chemotherapy-naive patients with advanced HNSCC, a CR of 5% and PR of 20% were reported in the combination cisplatin and fluorouracil group, with significant toxicities and no increase in survival.4 In the group treated with cisplatin alone, response rates were only 14%, and for fluorouracil alone, only 13%. In contrast, the trials reported herein were conducted in a patient population in whom multiple prior therapies, including systemic cisplatin, had failed. In this group, treatment with cisplatin/epinephrine gel resulted in a response rate of 29% with few systemic toxicities. These rates are not direct comparisons, however, because all measurable and assessable disease was evaluated in the study with systemic drugs, whereas individual tumor response was the focus of this study.

In this difficult setting of patients with recurrent or metastatic HNSCC, treatment with intratumoral cisplatin/epinephrine gel has shown a strong association of tumor response with clinical benefit. A relationship between response and benefit has not been previously demonstrated for systemic chemotherapy in patients with HNSCC. Intratumoral cisplatin/epinephrine gel may find a role in the current treatment regimen for patients with HNSCC who cannot be treated by surgery or radiotherapy alone or as an alternative to systemic chemotherapy. In this study,
we found cisplatin/epinephrine gel useful for patients with advanced disease who had unresectable tumors smaller than 20 cm³. Cisplatin/epinephrine gel produces fewer systemic adverse effects than traditional systemic chemotherapy. Local adverse events are generally amenable to treatment and conservative wound management. Appropriate anesthesia administered during and after the injection procedure should be part of a comprehensive pain management program for each patient.

In these phase III trials, intratumoral cisplatin/epinephrine gel was used as a single agent in recurrent or metastatic HNSCC. Avenues that warrant future investigation include the possible use of cisplatin/epinephrine gel in combination with other therapies (radiotherapy, surgery, and systemic chemotherapy) to preserve organ function and enhance clinical response. Preclinical investigations to support future clinical trials have included a report on the use of cisplatin/epinephrine gel to prevent local tumor growth after margin-positive resection and a report on radiosensitization by intratumoral cisplatin/epinephrine gel in combination with radiotherapy. Studies are in progress combining cisplatin/epinephrine injectable gel with systemic chemotherapy in the hope of attaining superior tumor control and preventing relapse at the sites of bulky disease.

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REFERENCES


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