

Phase II Study of the Efficacy and Safety of Cisplatin-Epinephrine Injectable Gel Administered to Patients With Unresectable Hepatocellular Carcinoma

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Purpose: To study the efficacy and safety of percutaneous cisplatin-epinephrine (CDDP-EPI) injectable gel in patients with localized unresectable hepatocellular carcinoma (HCC).

Patients and Methods: Eligible patients had histologically proven HCC, no prior treatment except for surgery, and no more than three tumors (each measured ≤ 7 cm, total tumor volume ≤ 200 cm³). They were treated percutaneously under ultrasound or computed tomography (CT) guidance, with up to 10 mL of CDDP-EPI gel (1 mL contains 4 mg of CDDP and 0.1 mg of EPI) per treatment and four treatments in 6 weeks to a maximum of eight treatments. The primary end points were tumor response, defined by change of percentage of tumor necrosis according to CT criteria, and safety. Survival parameters were secondary end points.

Results: From June 1997 to April 2000, 58 patients (median age, 65 years) entered the study. All patients were

assessable for safety, and 51 were assessable for efficacy. The median number of treatments was four (range, one to eight treatments). Objective response rate was 53% (27 of 51 patients), including 16 complete and 11 partial responses. Of the 27 responders, 14 (52%) subsequently developed progressive disease, but in most of them (93%), a new tumor arose at untreated liver sites. Median survival was 27 months (range, 18.4 to 35.7 months). The 1-, 2-, and 3-year survival rates were 79%, 56%, and 14% respectively. The procedure was well tolerated with only minor side effects.

Conclusion: Percutaneous local ablation with CDDP-EPI injectable gel can induce significant tumor necrosis and local control for localized unresectable HCC, and the treatment is well tolerated.

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HEPATOCELLULAR CARCINOMA (HCC) is the fifth most common cancer¹ and the most common fatal cancer worldwide. Approximately 315,000 cases of HCC are diagnosed each year, accounting for 4.1% of all new human cancer cases.² The highest incidence rates occur in Asia and Africa, where there is also a marked increase in younger aged groups,³ but both incidence and mortality rates are increasing in some countries in North America and Europe.^{4,5}

It is widely considered that the only potentially curative treatment of HCC is surgical resection. However, the majority of patients (75% to 90%) are not candidates for resection, either because of the presence of advanced disease, inadequate liver function (up to 80% of HCCs are associated with underlying cirrhosis), or both.⁶⁻⁹ Nonsurgical treatments for unresectable HCC include chemoembolization, systemic chemotherapy, and radiotherapy, but none has been found to prolong survival in

prospective randomized studies. The overall treatment results are poor, and prognosis of unresectable HCC remains dismal.

There is also increasing evidence to suggest that for patients with small localized tumors that are not resectable for various reasons, curative-intent treatment with liver transplantation or local ablative therapies is still possible.¹⁰ Local ablative therapy is usually performed under image guidance (either computed tomography [CT] or ultrasonography [US]) by means of ethanol injection,¹¹ radiofrequency ablation (RFA),¹² or microwave coagulation.¹³ These local treatments are indicated for small tumors (≤ 5 cm in diameter) and few lesions (three or less), and are used as primary treatment or as a temporalizing measure while waiting for liver transplantation. An effective local ablative modality should induce a high degree of tumor necrosis in the tumor with a margin but not be toxic to the surrounding liver parenchyma or structures. Local ablation with high concentrations of cytotoxic agents may be potentially toxic to cancer tissue. However, direct injection of cytotoxic drugs has not been practical in the past because the drug disperses rapidly into surrounding tissue and the systemic circulation shortly after injection.

In this study, we evaluated a new form of local intratumoral ablative chemotherapy with a modified-release drug-delivery system, which provides a high intratumoral concentration of cisplatin for extended periods, with significantly reduced systemic exposure.¹⁴⁻¹⁶ This novel drug, cisplatin-epinephrine (CDDP-EPI) injectable gel (Matrix Pharmaceutical, Inc, Fremont, CA), combines CDDP and EPI, a vasoconstrictive agent, in a biodegradable matrix made of purified, buffered, nonpyrogenic bovine collagen that acts a gellant.¹⁶ CDDP-EPI gel has been used to treat a variety of solid tumors.¹⁷ An earlier phase I study demonstrated the feasibility of injecting CDDP-EPI gel

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into liver tumors percutaneously under image guidance.¹⁸ The objective of this phase II open-label study was to examine the efficacy and safety of CDDP-EPI gel in the treatment of patients with localized unresectable HCC.

PATIENTS AND METHODS

This multicenter study was conducted in North America, Europe, and Asia. The test product was CDDP-EPI injectable gel; 1 mL of CDDP-EPI gel contains 4 mg of cisplatin and 0.1 mg of EPI.

Eligibility Criteria

Adult patients (≥ 18 years) with histologically confirmed, unresectable HCC with no extrahepatic or major vascular involvement and no prior therapy other than surgical resection were eligible for the study. Patients were required to have no more than three tumors, each with a diameter ≤ 7 cm and a cumulative total treated volume ≤ 200 cm³. Other inclusion criteria included the following: an adequate hematology profile (hemoglobin ≥ 10 g/dL, granulocyte count $\geq 1,000/\mu\text{L}$, platelet count $\geq 75,000/\mu\text{L}$); renal function (serum creatinine level ≤ 1.3 times the upper limit of reference range, or a creatinine clearance ≥ 45 mL/min); liver function (ALT and AST ≤ 3 times upper limit of reference range, albumin ≥ 2.5 g/dL, bilirubin ≤ 2.98 mg/dL, alkaline phosphatase ≤ 3 times the upper limit of reference range); clotting profile (prothrombin time within 3 seconds of control); Child-Pugh grade A or B; absent or easily controlled ascites requiring no paracentesis; an expected survival of at least 4 months; and the ability to provide written informed consent.

Patients were excluded if they exhibited any of the following: New York Heart Association Class III or IV cardiovascular symptoms; obesity; tumor location(s) that prevented adequate imaging of tumor(s); known hypersensitivity to cisplatin, bovine collagen, EPI, sulfites, or radiographic contrast agents; history of hepatic encephalopathy or bleeding gastroesophageal varices; and pregnancy, breast feeding, or reluctance to use adequate birth control. Patients who had received systemic chemotherapy, radiation, or other cancer therapies were not allowed to enter into the study. However, prior surgical resection for the primary lesion was allowed.

Treatment Plan

Up to three tumors were identified for treatment in each patient at the screening visit. Tumor volumes were assessed by contrast-enhanced, triphasic spiral CT scan. Each patient's dosage was estimated from the screening CT data by multiplying the prospective dose (0.5 mL CDDP-EPI gel/cm³ of tumor) by the total viable tumor volume of the one to three treated tumors (estimated as length \times width \times height $\times 0.5$) up to a maximum of 10 mL CDDP-EPI gel (40 mg of CDDP and 1 mg of EPI) per treatment visit. Distribution of the maximum dosage among the one to three tumors was left to the judgment of the physician.

Study treatment consisted of weekly intratumoral injections of CDDP-EPI gel to a maximum of four treatments within a 6-week period. Response was evaluated by CT scan at 2 weeks after treatment. At the discretion of the physician, a second four-treatment cycle within a 6-week period—for a maximum of eight treatments—was permissible but only for previously treated tumors. No new emergent tumors were treated during the study. Response was again evaluated at 2 weeks after treatment. If response occurred, CT scans were repeated within a 28- to 36-day period for confirmation. Patients who had a complete response (CR) or partial response (PR) to treatment were then observed monthly to monitor the duration of response; CT scans were repeated at 2, 4, and 6 months, and every 3 months thereafter while the objective response continued. All patients were observed for survival, including patients scheduled for liver transplantation.

Drug Administration

CDDP-EPI gel was administered intratumorally by percutaneous injection into the tumor, under US or CT guidance, using a 22- to 25-gauge needle on a Luer-lock syringe. The gel was injected in a fanning grid, or multiple-tracking manner, in rows approximately 1 cm apart to disperse the drug uniformly throughout the treated tumor while avoiding placement into or next to a blood vessel. The dose was injected slowly in 2.5-mL increments,

each followed by a 5-minute pause to monitor for any significant changes in vital signs. This process continued until the assigned maximum dosage of 10 mL or tumor capacity was reached.

Systemic hydration was administered before injection. Local anesthetics, local-regional nerve blocks, and systemic agents could be used for pain control; however, anesthetics containing EPI were prohibited. Concurrent systemic chemotherapy, other investigational cancer therapy, immunomodulators, or drugs that interact with CDDP (eg, probenecid and thiazide) were prohibited during the treatment or re-treatment phases. Pretreatment anxiolytics and analgesics could be used to manage anxiety or transient hypertension.

Efficacy Evaluation

The primary efficacy end point was objective tumor response. Secondary end points included time to response, number of treatments to onset of response, duration of response, and patient survival. Treated tumors were measured by US or CT imaging after each treatment cycle. Tumor response was assessed by percent change in total viable tumor volume (calculated as total treated tumor volume minus total necrotic tumor volume).

Response to treatment was defined as change in viable tumor volume sustained for ≥ 28 days and rated as follows: CR, 100% decrease in baseline viable tumor volume; PR, at least 50% but less than 100% decrease in baseline viable tumor volume; stable disease, less than 50% decrease or less than 25% increase in baseline viable tumor volume; and progressive disease, 25% or greater increase in baseline viable tumor volume at any time on study. Any appearance of new lesions was considered to be progressive disease. Objective response was defined as CR or PR; nonresponse was defined as stable disease or progressive disease.

Safety Evaluation

Safety, evaluated at each study visit, included a brief physical examination, clinical laboratory evaluations, and assessments of intercurrent illness (including toxicities) and adverse events. The presence and severity of seven symptoms commonly reported by patients with liver tumors (ie, ascites, anorexia, jaundice, local pain, anergy or lack of energy, malaise or bodily discomfort-fatigue, and intratumoral hemorrhage) were assessed at every visit. Adverse events after treatment were divided into two categories, namely treatment site and systemic adverse events. Treatment site adverse events included immediate events, which occurred during the first 15 minutes after injection, and after-injection events, which occurred after the first 15 minutes after injection. Systemic adverse events included all adverse events not occurring at the treatment site. Data regarding the start and stop dates for all adverse events, the degree of severity (according to the National Cancer Institute Common Toxicity Criteria), and the causal relationship to study drug were collected at each visit.

Statistical Analyses

Statistical analyses were performed for the following variables: response of treated tumors, time to and duration of response, time to progression, patient survival, volume and dose of CDDP-EPI gel, and number of doses to objective response. Survival times were not censored for confounding therapy with the exception of patients who underwent liver transplantation. Time to progression and survival time were estimated using the Kaplan-Meier method (SAS Institute, Cary, NC). Safety analyses included all treated patients. Presence and severity of seven common tumor symptoms were collected at each study visit. The baseline prevalence, time to onset or worsening, and duration were summarized for all patients.

RESULTS

Patient Characteristics

Between June 1997 and April 2000, 58 patients with unresectable primary HCC were enrolled onto this open-label, phase II clinical trial. Fifty-one patients were included in the per-protocol efficacy analyses. Of the seven patients excluded from the efficacy analyses, one patient never received drug because of inaccessibility of the tumor, one had insufficient evidence of

Table 1. Patient Characteristics

Characteristic	No. of Patients	%
No. of patients enrolled	58	
No. of patients assessable	51	
Age, years		
Median	65	
Range	37-81	
Sex		
Male	37	
Female	14	
Ethnicity		
White	27	
Asian	22	
Other	2	
Karnofsky performance status		
Median	100	
Range	70-100	
Underlying liver disease		
Cirrhosis	49	96
Child-Pugh grade A	13	25
Child-Pugh grade B	38	75
AFP, ng/mL		
Median	33	
Range	2-918	
Prior therapy, surgery	11	22
Contraindications to surgery		
Advanced cirrhosis	18	35
Poor liver function	11	21
Multifocal tumors	10	20
Comorbid disease or intercurrent illness	7	14
Advanced age	5	10
Viable baseline tumor volume, cm ³		
Median	25	
Range	2-314	

Abbreviation: AFP, alpha-fetoprotein.

HCC at screening, one had a benign regenerative nodule treated, three patients died within 28 days after their first treatment visit, and one patient entered the study with ascites and elevated bilirubin levels and was discontinued immediately after the first visit.

Patient characteristics are listed in Table 1. The majority of the patients (96%) had cirrhosis, 78% associated with chronic hepatitis B or C infection. Three quarters of the patients were classified as Child-Pugh grade B, and the rest were classified as grade A. Eleven patients (22%) had had prior surgery for HCC. However, all patients were deemed unsuitable candidates for surgical intervention for one of the following reasons: cirrhosis (n = 18), inadequate liver function (n = 11), multifocal tumors (n = 10), intercurrent illness (n = 7), and advanced age (n = 5).

Tumor Response and Survival

The median total viable tumor volume per patient at baseline was 25 cm³ (range, 2 to 314 cm³). Variation was noted in tumor size by the following geographic areas: Europe, median tumor size, 41 cm³ (range, 3 to 314 cm³); United States, median tumor size, 22 cm³ (range, 2 to 240 cm³); and Asia, median tumor size, 17 cm³ (range, 2 to 98 cm³). As shown in Table 2, 27 (53%) of 51 patients responded to treatment, and the majority of those were CRs (59%, 16 of 27 patients). The median time to onset of response documented by CT scans was 1.8 months (range, 0.04

Table 2. Patient Response Rates (n = 51)

	No. of Patients	%
Objective response*	27	53
Complete	16	31
Partial	11	22
Stable disease	18	35
Progressive disease	5	10
Not assessable	1	2
Total number of treatments		
Median	4	
Range	1-8	
Duration of response, months		
Median	9.5	
Range	4.3-32.3	

*Complete response + partial response: 95% confidence interval, 0.39 to 0.67.

to 5.8 months) after a median of four treatments. The median duration of response was 9.5 months (range, 4.3 to 32.3 months). Individual features of patients who responded are listed in Table 3.

Twenty-nine (57%) of 51 patients received between one and four treatments, and 15 (52%) of 29 had objective responses. Of the patients who continued on to receive additional treatments (one patient received five treatments, six received six treatments, and 15 received eight treatments), 12 (55%) of 22 patients responded. During cycle 1 (one to four treatments), dose levels ranged from 8 to 9 mL (32 to 36 mg CDDP, respectively); during cycle 2 (five to eight treatments), the dose levels ranged from 7.3 to 8.1 mL (32 to 40 mg CDDP, respectively). The cumulative median dose for all patients was 36.5 mL of gel (range, 2.5 to 80 mL) and 146 mg of CDDP (range, 10 to 320 mg).

Of the 27 patients who responded to treatment with CDDP-EPI gel, 14 subsequently had progressive disease (Table 4). The dominant pattern of progression was new tumors appearing in the untreated liver (79%, 11 of 14 patients). Only one of the responding patients (4%) experienced recurrence at a treated site, and two patients (14%) had only extrahepatic progression. Most of the disease progression in patients who had a response or stable disease was limited to the liver only (83%, 20 of 24 patients).

The median survival for all 51 assessable patients was 27 months (range, 18.4 to 35.7 months). The 1-, 2-, and 3-year survival rates were 79%, 56%, and 14% respectively. The Kaplan-Meier actuarial survival curve for all the patients is shown in Fig 1.

Histologic Confirmation of Tumor Response

The pathology of six treated lesions in three patients was examined histologically. Two patients received orthotopic liver transplantation after treatment, and the third patient had an autopsy (Table 5). Histologic examination of the explanted livers showed extensive necrosis (80% to 100%) in five of six lesions treated with CDDP-EPI gel, and small foci of necrosis in one lesion. Five lesions had posttreatment CT assessments, and in three of these five lesions, there was a good correlation between the CT scans and histologic examination with respect to degree of necrosis. However, for one lesion, the CT evaluation greatly underestimated the degree of necrosis (CT scan shows only 10%

Table 3. Individual Case Features of Patients with Complete Response (n = 16)

Patient No.	Response	No. of Treated Tumors	No. of Treatments	Baseline Tumor Volume (cm ³)	Time to Response (weeks)	Duration of Response (weeks)	Progression After Response (yes/no)
1	CR	1	4	36.3	—	46.1	No
		2	4				
		3	4				
2	CR	1	8	8.7	18.0	OLT	No
		2	7				
3	CR	1	8	19.2	6.0	17.0	No
		2	8				
4	CR	1	8	38.0	7.0	89.7	No
		2	8				
5	CR	1	4	38.6	7.6	37.1	No
		2	4				
6	CR	1	1	4.6	2.4	27.1	No
7	CR	1	4	7.5	7.1	79.0	No
8	CR	1	4	25	13.1	63.7	No
9	CR	1	4	21.3	5.9	70.6	No
10	CR	1	4	1.5	7.0	76.4	No
11	CR	1	4	5.6	10.0	32.4	No
12	CR	1	4	67.5	6.3	22.9	No
13	CR	1	6	3	7.0	99.3	No
14	CR	1	8	11.7	10.0	27.3	No
15	CR	1	8	27.3	7.0	25.3	No
16	CR	1	8	24.8	7.0	34.3	No

Abbreviations: CR, complete response; OLT, orthotopic liver transplantation.

necrosis), which was actually a complete necrosis by histologic examination.

Safety

At each visit, physicians were required to evaluate seven symptoms commonly reported for patients with liver tumors (ie, anergy, anorexia, ascites, jaundice, local pain, malaise, and intratumoral hemorrhage). Intratumoral hemorrhage was neither present at baseline nor did it occur in any patients during the study. In general, the other six symptoms remained unchanged during treatment. Table 6 lists the adverse events related to treatment with CDDP-EPI gel. Hypertension (17%) was the most common event during or immediately after injection (< 15 minutes), followed by injection pain (16%) and tachycardia

(10%); these events were generally transient and rarely severe. After injection (> 15 minutes after), pain at the treatment site was experienced by 41% of patients and abdominal pain was experienced by 21% of patients, and both were generally mild to moderate. The most common systemic events were fever (48%), vomiting (24%), asthenia (24%), nausea (22%), and chills (22%); most of these were considered to be mild or moderate.

During this study, three of 29 deaths were considered to be either possibly related or related to study drug (25 were unrelated to treatment, and in one patient, the relationship is unknown). One patient with a history of intravenous drug abuse and severe liver cirrhosis died 1 day after treatment because of rupture of the hepatoma; the death was considered to be possibly related to the study drug. Another self-admitted drug abuser with an

Table 4. Pattern of Progression in Patients Who Had Progressive Disease After Having Objective Responses or Stable Disease (n = 24)

Sites of Progression	No. of Patients	
	CR + PR (n = 14)	SD (n = 10)
Intrahepatic progression only		
Progression at any treated site	0	3
New tumors in liver, not at treated site	11	5
Both progression at any treated site and new tumors in liver	1	0
Extrahepatic progression only	0	2
Extrahepatic and intrahepatic progression		
Progression at any treated site and any extrahepatic progression	0	0
New tumors in the liver, not at treated site, and extrahepatic progression	2	0
Progression at any treated site, new tumors in the liver, and extrahepatic progression	0	0

Abbreviations: CR, complete response; PR, partial response; SD, stable disease.

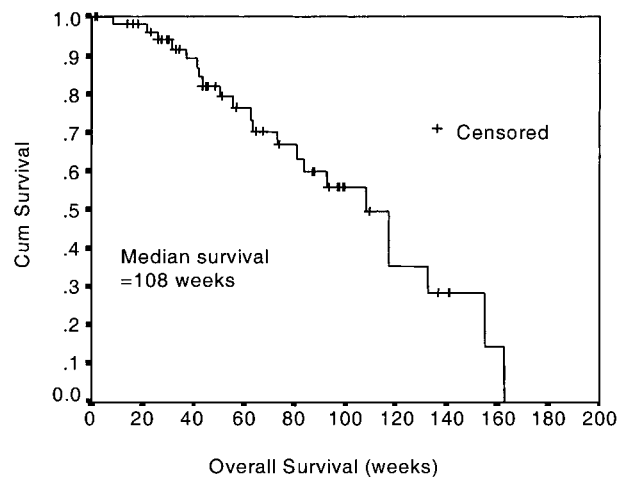


Fig 1. Actuarial survival curve.

Table 5. Histopathologic Confirmation of Tumor Response

Patient	Tumor No.	CT Assessment* Before Treatment		CT Assessment After Treatment		Histopathologic Findings
		Volume (cm ³)	Necrosis (%)	Volume (cm ³)	Necrosis (%)	
I†	1	23.6	0	—	100	Complete necrosis
	2	2.1	0	—	40	Small foci of necrosis
	3	1.1	0	—	90	Complete necrosis
II†	1	3.8	0	—	10	Complete necrosis
	2	4.9	0	—	80	Complete necrosis
III‡	1	15.8	8	—	Not performed	Approximately 75% necrosis

Abbreviation: CT, computed tomography.

*Calculated manually from CT measurements.

†Orthotopic liver transplantation.

‡Autopsy: patient died before completing one cycle of treatment.

extensive medical history, including hepatic perforation from a gunshot wound, died on the day of his third treatment, and the possibility of hypersensitivity reaction was investigated; the death was considered possibly drug related. Another patient with esophageal varices, chronic hepatitis, and cirrhosis lapsed into coma from hepatic failure 1 week after treatment; although the physician deemed the event not related to drug, the study sponsor considered that a contributory effect could not be ruled out. Ten other patients had adverse events that were considered serious; nine recovered without sequelae, and one patient was hospitalized with profound abdominal pain and vomiting, and treatment was terminated.

DISCUSSION

With the improvement in imaging modalities for small hepatic lesions and screening programs for high-risk individuals (those

with chronic liver disease or who are carriers of hepatitis B or C), it is likely that more cases of HCC will be diagnosed at an early stage. These early HCCs are often localized to the liver and are potentially curable with surgery. However, not all are amenable to surgery because of limited liver reserve. Currently, local ablation with ethanol or thermal treatment (RFA or microwave coagulation) can be effective, and they are the choice of treatment if the tumor size is small and the number of lesions few.¹⁰ For tumors less than 5 cm, the percentage of necrosis after microwave coagulation or RFA is more than 90%.^{19,20} From a recent prospective study on 102 patients randomized to either RFA or ethanol injection for tumors less than 5 cm, the 2-year survival rates for RFA and ethanol injection were 98% and 88%, respectively.²¹ Although the overall survival has no significant difference, the recurrence-free survival was longer for the RFA arm, which was statistically significant.²¹ For patients with even smaller tumors (< 2 cm) treated with either ethanol injection or microwave coagulation, the 5-year survival rate was 78%.²² These treatment results are actually quite comparable with surgical resection.

However, for lesions that are close to the main portal vein, heart, or intestine, thermal ablation may not be feasible. Heat carried away by the high blood flow in the region (heat sink problem) damps down the thermal effect. Heat may also cause damage to nearby vital organs. In these circumstances, percutaneous ethanol or intratumoral drug injection can be an option. However, the efficacy of ethanol injection is probably inferior to RFA in terms of percentage of tumor necrosis and survival,^{21,23} which is probably because ethanol can disperse easily if it gets into relatively large blood vessels. It is also difficult to see where the ethanol stays by imaging methods, and the volume of ethanol used is quite arbitrary. An improved intratumoral drug delivery system, which can induce a high degree of tumor necrosis, is visible under an imaging modality, and has a good safety profile, can be the choice of treatment for patients not suitable for thermal ablation or for patients in places where thermal ablation is not available.

Intratumoral injection of cytotoxic drugs for treatment of localized cancer was not successful until an improved delivery system was developed that allows slow release of the drug into the tumorous tissue.¹⁵ The CDDP-EPI injectable gel was the first such approach to be successfully developed and taken to clinical trials for gastric, esophageal, head and neck, metastatic liver, and

Table 6. Treatment-Related Adverse Events Occurring in ≥ Three Patients (N = 58)

Event	Mild/Moderate		Severe	
	No.	%	No.	%
Events at treatment site				
Immediate, during or within 15 minutes of injection				
Hypertension	7	12	3	5
Pain at treatment site	7	12	2	3
Tachycardia	4	7	2	3
After injection, ≥ 15 minutes after injection				
Pain at treatment site	22	38	2	3
Abdominal pain	8	14	4	7
Systemic events				
Fever	27	47	1	2
Asthenia	13	22	3	5
Vomiting	13	22	1	2
Nausea	13	22	0	0
Chills	11	19	1	2
Anorexia	10	17	1	2
Abdominal pain	6	10	0	0
Malaise	7	12	3	5
Headache	6	10	0	0
Pain, general	6	10	0	0
Dizziness	4	7	0	0
Hypotension	3	5	1	2
Contusion	3	5	0	0
Edema, peripheral	3	5	0	0
Hypertension	3	5	0	0
Ascites	2	3	2	3

breast cancers and melanoma.^{18,24-30} In this study, a uniform cohort of patients with treatment-naïve, localized, unresectable HCC was treated with intratumoral CDDP-EPI injectable gel; activity of the compound with respect to induction of tumor necrosis was demonstrated.

Histologic examination of six treated lesions from three patients was performed. Five of these lesions showed either complete or nearly complete necrosis, and in three of five lesions, this was confirmed by the CT findings. In addition, evidence of tumor necrosis after treatment with CDDP-EPI gel is supported by a magnetic resonance imaging (MRI) evaluation of a subset of 11 patients (17 lesions) from this study.³¹ Viable tumor volume and degree of necrosis were examined before and after treatment using turbo spin-echo MRI, including a dynamic study of gadolinium-enhanced T1-weighted sequences. MRI showed no viable tumor in 15 (88%) of 17 lesions and only 11% and 15% viable tumor in the two remaining lesions. The effect of direct intratumoral injection of CDDP-EPI gel on tumor cell death has also been studied in a rabbit model of liver cancer.³² Percent tumor necrosis as measured by histology was 85% in tumors receiving two injections and 75% in tumors receiving one injection versus 52% for control lesions with no treatment. The fraction of tumor necrosis estimated by contrast-enhanced CT imaging correlated well with that found by histologic examination.

Although these lesions may have shown only static disease according to conventional radiologic response criteria, extensive necrosis was documented, indicating activity of the compound. The extent of tumor necrosis and changes in degree of contrast enhancement in CT scans after treatment have been widely used as an index of response in other forms of local ablative therapies.²⁰⁻²³ From our study, we confirmed by histology that such an approach is valid. This may have implications for new compounds put into clinical trials; conventional response criteria focusing on changes in size of lesion may not reflect the true activity of the drug.

The objective response rate was 53% (25 of 51 patients), including 16 CRs and nine PRs. Five out of the 16 patients with CR have relatively small-volume disease, but they had unresectable disease before entering onto the study. The reason for unresectability was because of advanced liver cirrhosis. Although liver resection is still considered to be curative for early-stage and small-volume disease, it is often not feasible because of poor liver function.

Treatment-related adverse events were mainly local pain and fever. These symptoms were usually mild or moderate in severity, and their duration was brief. Severe side effects were uncommon. Approximately 5% of patients had a significant increase in blood pressure during treatment. This can be ex-

plained by apprehension of the treatment and can easily be treated by anxiolytics before treatment. Hypertension was, however, severe in three patients and is likely a result of EPI reaching the systemic circulation through the hepatic vein. Although the drug distribution within the tumor can be visualized by imaging methods during the injection procedure, it is not possible to preclude the occasional venous uptake of EPI released from the gel preparation.

Some patients experienced nausea and vomiting during and after treatment, which is probably a result of premedications or the emetogenic effect of the CDDP. A simple antiemetic agent is all that was required to control vomiting. Caution was required when treating large vascular tumors that were close to the liver surface because of the risk of rupture. This happened in one of the studied subjects in this study. In another patient who had an autopsy performed, collagen fibrils were retrieved from the pulmonary vasculature. This can be explained by shunting of the collagen material from the treated lesion to the lungs through abnormal arteriovenous shunt. Therefore, patients with large arteriovenous shunts as demonstrated by imaging or angiogram should not be considered for this treatment.

One of the unique features of the CDDP-EPI gel is that it is readily visible under US because of the echogenic nature of the gel. This can aid the physician in proper placement of the therapy, make it easier to determine how much drug is placed in the tumor, and allow the physician to get closer to margins. Because it does not involve heat, and the extent of drug infiltration is clearly visible, less irritation of the liver capsule and, hence, less pain may be caused than with other local ablative therapies.

Most of the failure of treatment is because of new tumors occurring in the untreated sites. This is no different from other local ablative therapies, including surgery. A study from Japan showed that the recurrence-free survival rate for percutaneous ethanol injection or microwave coagulation was 30% to 39% at 4 years, and most recurrences are intrahepatic.²² Further treatment of new lesions with CDDP-EPI gel is possible and should be investigated in subsequent studies.

In conclusion, we found that intratumoral injection of CDDP-EPI gel is effective for localized unresectable HCC. Side effects are tolerable. CDDP-EPI gel can be an option for lesions not suitable for thermal ablation or in places where thermal ablation is not available.

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