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Evaluation on Short-Term Therapeutic Effect of 2 Porphyrin Photosensitizer-Mediated Photodynamic Therapy for Esophageal Cancer

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Abstract

Purpose: To analyze and study the short-term therapeutic effects and main adverse effects of 2 Porphyrin photosensitizer-mediated photodynamic therapy for esophageal cancer. **Methods:** We apply the hematoporphyrin derivative and hematoporphyrin injection produced by different manufacturers at different periods as photosensitizers in therapy of 79 esophageal cancer cases, with the administration dosage of 5 mg/kg and intravenous drip 24 hours before irradiation. We apply the gold vapor laser and semiconductor laser, respectively, as treatment light source, with the power density of 100 to 300 mW/cm^2 and energy density of 100 to 300 J/cm^2. After treatment for 1 to 4 sessions, we evaluate the short-term therapeutic effects as complete response, partial response, minor response, or no change, and then make comparative study on therapeutic effects and adverse effects. **Results:** There were 47 patients in hematoporphyrin derivative group, including 3 (6.4%) patients with complete response, 31 (66.0%) patients with partial response, 10 (21.3%) patients with minor response, and 3 (6.4%) patients with no change. The dysphagia score was reduced from 2.53 (1.16) before treatment to 1.32 (1.20; $P < .01$) after treatment. There were 32 patients in the hematoporphyrin injection group, including 3 (9.4%) patients with complete response, 19 (59.4%) patients with partial response, 6 (18.8%) patients with minor response, and 4 (12.5%) patients with no change. The dysphagia score was reduced from 2.41 (1.13) before treatment to 1.18 (0.99; $P < .01$) after treatment. The dysphagia scores of 2 groups after treatment were significantly reduced compared to those before treatment. Both groups did not display serious adverse effect. **Conclusions:** Two porphyrin photosensitizers in treatment of esophageal cancer at different clinical stages all had good effect with similar therapeutic effect, mild adverse effect, and good tolerance, which implies it is a preferable palliative therapy means.

Keywords

photodynamic therapy, esophageal cancer, dysphagia, photosensitizer, laser

Abbreviations

CR, complete response; Hp, hematoporphyrin; MR, minor response; NC, no change; HpD, hematoporphyrin derivative; PDT, photodynamic therapy; PR, partial response

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Introduction

The present data show that esophageal cancer of about 40% to 50% of patients is surgically unresectable while diagnosed. Despite progress in both diagnosis and treatment of esophageal cancer, the 5-year survival rate continues to be less than 10%.[1,2] For patients with advanced esophageal cancer, the dysphagia is

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the most prominent clinical problem.[3] Patients have very poor quality of life due to pain, fatigue, and not being able to swallow. The prompt improvement in swallowing in patients promotes the nutritional state, improves physical conditions, relieves the psychological pressure, enhances the quality of life, and may facilitate comprehensive therapy that follows.[4]

Multimodality therapy, consisting of external beam irradiation,[5] brachytherapy,[6] dilation,[7] argon plasma coagulation,[8] chemotherapy,[9] esophageal prosthesis,[10] and photodynamic therapy (PDT), has been used as a palliation therapy for esophageal cancer. Photodynamic therapy is an important technology of minimally invasive treatment for tumor. Its effectiveness and safety have been sufficiently proved in clinical work. And it has been recommended as radical therapy for early esophageal cancer and palliative therapy for advanced esophageal cancer in various tumor therapeutic guidelines.[11,12]

In China, hematoporphyrin derivative (HpD), as the first generation of photosensitizer, plays a very important role in development and progress of PDT.[13] We had successively applied 2 porphyrin photosensitizers (all are HpDs) produced by 2 companies for therapy of 79 cases with esophageal cancer from February 1997 to October 2014, and gained good short-term therapeutic effects. Two photosensitizers were found to have good inheritance. Now the analysis report is as follows.

Methods

Clinical Data

Seventy-nine patients with esophageal cancer were confirmed by the pathological examination. None was eligible for surgical resection due to local invasion, distant lymph node metastasis, poor physical condition, comorbidity, refusal of surgical intervention, recurrence after surgery, or a combination of the above reasons. The baseline characteristics of the patients are shown in Table 1. The pretreatment performance status ECOG score is $\geq$2. All patients have signed the informed consent.

Photosensitizers and Lasers

From February 1997 to August 2003, HpD produced by Beijing Pharmaceutical Industry Research Institute had been applied, and the supporting laser had adopted IEAu-3 type gold vapor laser provided by Institute of Electronics, Chinese Academy of Sciences, with the laser wavelength of 627.8 nm and total output power of 1000 mW. From September 2010 to October 2014, hematoporphyrin (Hp) injection produced by Chongqing Huading Modern Biopharmacy Co, Ltd (Chongqing, China) had been applied, and the supporting laser had adopted PDT630 laser tumor therapeutic apparatus produced by Guilin Xingda Photoelectric Medical Instrument Co, Ltd (Guilin Guangxi, province of China), with laser wavelength of 630 nm and total output power of 2000 mW. The photosensitizers were kept out of the light and at -20°C.

Table 1. Baseline Characteristics of the Patients.

Characteristics	HpD group	Hp group
Case (n)	47	32
Age (years)		
Mean	65	67
Range	25-84	31-88
Sex		
Male	35 (74.5)	22 (68.8)
Female	12 (25.6)	10 (31.3)
ECOG score		
Mean	1	1
Range	0-2	0-2
Focus location		
Esophagus squamous cell carcinoma	25 (53.2)	21 (65.6)
Gastroesophageal junction adenocarcinoma	22 (46.8)	11 (34.4)
Focus status		
Initial local disease	6 (12.8)	4 (12.5)
Recurrent local disease	30 (63.8)	19 (59.4)
Metastasis	11 (23.4)	9 (28.1)

Abbreviation: HpD, hematoporphyrin derivative.

Therapeutic Method

Two photosensitizers were applied for the dermal sensitivity test before administration, and 100 mL normal saline injection was added to negative patients by administration dosage of 5 mg/kg via intravenous drip. At 24 to 72 hours after administration, guided by the endoscope, optical quartz fiber was led by biopsy hole, to align at the lesion location and irradiate for 1 time every day, totaling to 3 times. While irradiating, it is required to keep all parts of focus having uniform injectivity to the greatest extent. Patients with longer focus were irradiated by sections from distal to proximal. Each section of focus is overlapped during irradiation, and the outermost edge should be at least 0.5 cm away from the focus edge, to make the facula cover the focus fully. The power density is 100 to 300 mW/cm^2, and the energy density is 100 to 300 J/cm^2. The selection of treatment parameters depends on patients' conditions. Patients at the early stage should be treated by the low power and low energy density, and patients with obvious obstruction at the progressive stage should be treated with higher power and energy density.

For the patients with serious obstruction, if optical fiber fails to lead, local microwave scorching should be used to remove the tumor tissue, to enable insertion of the optical fiber. Patients should stay out of the sun after photosensitizer administration. Clear liquid was started on the first day following the initial PDT treatment. Patients remained on a liquid diet until completion of the PDT treatment. If they could tolerate it, all patients were advanced to a soft diet 2 to 3 days after PDT treatment.

Gastroscopy was reviewed to determine the therapeutic effects within 4 weeks after treatment. Based on the patients' condition, the treatment of the next session was conducted more than 6 weeks after the first treatment.

Table 2. The Therapeutic Effect of HpD.

Tumor Location	Number of Cases, n (%)	CR	PR	MR	NC	ORR (CR + PR)
		Number of Cases, n (%)	Number of Cases, n (%)	Number of Cases, n (%)	Number of Cases, n (%)	Number of Cases, n (%)
Esophagus	25	2 (8.0)	15 (60.0)	7 (28.0)	1 (4.0)	17 (68.0)
Gastroesophageal junction	22	1 (4.5)	16 (72.7)	3 (13.6)	2 (9.1)	17 (77.3)
Total	47	3 (6.4)	31 (66.0)	10 (21.3)	3 (6.4)	34 (72.3)

Abbreviations: CR, complete response; HpD, hematoporphyrin derivative; MR, minor response; NC, no change; PR, partial response.

Table 3. The Therapeutic Effect of Hp.

Tumor Location	Number of Cases, n (%)	CR	PR	MR	NC	ORR (CR + PR)
		Number of Cases, n (%)	Number of Cases, n (%)	Number of Cases, n (%)	Number of Cases, n (%)	Number of Cases, n (%)
Esophagus	21	3 (14.3)	13 (61.9)	3 (14.3)	2 (9.5)	16 (76.2)
Gastroesophageal junction	11	0 (0)	6 (54.5)	3 (27.3)	2 (18.2)	6 (54.5)
Total	32	3 (9.4)	19 (59.4)	6 (18.8)	4 (12.5)	22 (68.8)

Abbreviations: CR, complete response; MR, minor response; NC, no change; PR, partial response.

Evaluation on Therapeutic Effects

Dysphagia was graded using the following scale: grade 0, asymptomatic; grade 1, difficulty in swallowing solid food; grade 2, difficulty in swallowing semisolid food; grade 3, difficulty in swallowing liquids; grade 4, inability to swallow anything, including saliva.

Evaluation standard on therapeutic effects: Complete response (CR): tumor completely disappeared, and pathologic biopsy was negative, lasting for more than 4 weeks. Partial response (PR): dysphagia score upgraded at least one degree, but failed to reach CR standard, lasting for 4 weeks. Minor response (MR): swallowing condition improved, but dysphagia score was not upgraded one degree, lasting for 4 weeks. No change (NC): tumor was not changed, and dysphagia score was not relieved or aggravated.

Statistical Analysis

According to the dysphagia scores classification of patients, the improvement of esophageal obstruction of patients before and after treatment was calculated. SPSS statistical software 20.0 was applied for the statistical analysis. All values were reported as the mean (standard deviation, SD). Differences in dysphagia scores were analyzed using a paired Student *t* test; *P* values of <.05 were considered to be statistically significant.

Results

Clinical Therapeutic Effects

Of 47 patients in the HpD group, 28 received 1 session of PDT, 11 received 2 sessions of PDT, 5 received 3 sessions of PDT, and 3 received 4 sessions of PDT. The therapeutic effect was evaluated for 4 weeks after treatment, that is, 3 (6.4%) patients with CR, 31 (66.0%) patients with PR, 10 (21.3%) patients with MR, and 3 (6.4%) patients with NC. The overall response rate (CR + PR) was 72.3% (see Table 2).

Of 32 patients in the Hp group, 25 received 1 session of PDT, 5 received 2 sessions of PDT, and 2 received 3 sessions of PDT. The therapeutic effect was evaluated for 4 weeks after treatment, that is, 3 (9.4%) patients with CR, 19 (59.4%) patients with PR, 6 (18.8%) patients with MR, and 4 (12.5%) patients with NC (see Table 3). The overall response rate (CR + PR) was 68.8% (see Table 3). One patient with esophageal cancer invasion of muscularis propria was cured by two sessions of PDT (see Figure 1).

In 2 groups of cases, some patients had transient dysphagia aggravation due to tumor tissue necrosis and edema in a short time after treatment, but the dysphagia of most patients improved after treatment for 1 week. In reference to our dysphagia score classification, the therapeutic effect was evaluated for 4 weeks after treatment. In the HpD group, the dysphagia scores of 16 patients were reduced by 1 degree, the dysphagia scores of 13 patients were reduced by 2 degrees, and the dysphagia scores of 5 patients were reduced by 3 degrees. The dysphagia score was reduced from 2.53 (1.16) before treatment to 1.32 (1.20) after treatment ($P < .01$). In the Hp group, the dysphagia scores of 8 patients were reduced by 1 degree, the dysphagia scores of 11 patients were reduced by 2 degrees, and the dysphagia scores of 3 patients were reduced by 3 degrees. The dysphagia score was reduced from 2.41 (1.13) before treatment to 1.18 (0.99) after treatment ($P < .01$). The dysphagia scores of 2 groups of patients after treatment were significantly reduced compared to those before treatment, but the 2 groups did not have significant difference (see Table 4).

Adverse Effect

In general, adverse effects in 2 groups of patients were mild and controllable. There were no serious adverse effects, such as

Table 4. Comparison of the Dysphagia Score of Esophageal Cancer With 2 Photosensitizers.

	HpD Group		Hp Group	
Dysphagia Score	Before Treatment	After Treatment	Before Treatment	After Treatment
Grade 0	3	14	3	8
Grade 1	6	16	3	14
Grade 2	11	7	8	7
Grade 3	17	8	14	2
Grade 4	10	2	4	1
P value	<.01		<.01	

Abbreviation: HpD, hematoporphyrin derivative.

Table 5. General Adverse Effect in 2 Groups.

	HpD Group	Hp Group
Adverse Effect	Number of Cases, n (%)	Number of Cases, n (%)
Epigastric and retrosternal pain	24 (42.1)	15 (50.0)
Fever	8 (17.0)	7 (21.9)
Skin photosensitivity	3 (6.4)	1 (3.1)
Skin color darken	15 (31.9)	10 (31.3)
Anaphylactic response	1 (2.1)	0 (0)
P value	>.05	

Abbreviation: HpD, hematoporphyrin derivative.

hemorrhage, perforation, tracheoesophageal fistula, or esophageal mediastinal fistula. Table 5 also shows that there was no significant statistic difference between HpD and Hp groups in terms of adverse effects. Twelve hours after treatment, some patients had a fever, and the temperature was generally below 38.5°C, lasting 3 to 5 days at the most. The temperature returned to normal after conventional treatment. Some patients had obvious epigastric and (or) retrosternal discomfort or pain; and some received analgesic treatment in severe cases. But in general, the pain was relieved within 3 to 7 days. In 2 groups, 4 patients failed to stay out of the sun as required, resulting in the skin swelling, pruritus, and pricking, and the symptoms disappeared after staying out of the sun strictly, while the skin color of 4 patients with skin photosensitivity was darkened temporarily. The skin color of nearly one-third of patients kept darkening at the end of staying out of the sun, though became lighter gradually after 3 months. Only 1 patient with HpD had the suspicious allergic reaction, manifesting as mild rash at the back, and got full recovery after treatment. None of the patients had treatment-related myelosuppression, or hepatic or renal function impairment; and electrocardiography did not have significant changes before and after treatment (see Table 5).

Discussion

In recent years, the incidence of cancer and cancer-related deaths has been increasing significantly in China, and new cases of cancer accounted for about 22% of the global total. Twenty-seven percent of cancer death cases were in China. The data of upper gastrointestinal tract cancer were more startling. The patients with gastric cancer accounted for 42% of the global total, and the annual number of deaths was about 340 000. The patients with esophageal cancer accounted for 50% of the global total, and the annual number of deaths was more than 250 000.[14]

Despite of the progress in both diagnosis and treatment of esophageal cancer, many patients were advanced while diagnosed and were unsuitable for the surgical treatment. The local focus control of some patients was still unsatisfactory even with the active treatment. Other patients were either unsuitable or reluctant to carry out the surgical operation, or chemoradiotherapy due to nontumorous reasons. Photodynamic therapy, as a minimally invasive therapy technology, had good palliative effect for the advanced patients, and the patients at the early stage may be treated more radically.[15,16]

In China, RECIST standard has always been adopted to evaluate the therapeutic effects of PDT, but for such hollow organ as esophagus, the evaluation on therapeutic effect was almost an impossible mission pursuant to the above standard. In reference to the literature of international PDT use in esophageal cancer treatment,[17] we deem the dysphagia improvement conditions of patients as one of the main indexes of therapeutic effects. The new evaluation standard on therapeutic effects accurately reflected the improvement in PDT for patients with esophageal cancer and reflected the beneficial degree of patients for treatment better.[18] In March 2014, our evaluation standard on PDT therapeutic effects of advanced upper gastrointestinal tract cancer was adopted jointly by Laser Medicine Branch of Chinese Medical Association and PDT Expert Committee of Chinese Society of Clinical Oncology as the national standard for popularization and application to solve the problems of difficulty in evaluation on PDT therapeutic effect of upper gastrointestinal tract cancer perplexing the Chinese academic society for many years at one stroke, and become the main evaluation index of therapeutic effect for PDT clinical study of upper gastrointestinal tract cancer at present.

The first generation of photosensitizer HpD is the father of modern photosensitizer, and it is widely used all over the world. In the past 30 years, many commercial HpD products could be used clinically, and tens of thousands of patients received PDT treatment. Hematoporphyrin derivative is a mixture photosensitizer, involving monomer, dimer, and oligomer, and all of these components possess the similar photosensitive effects. The research shows that HpD produced by different manufacturers has different preparation technologies, so the contents of above effective components are different, but the clinical effects are similar.[13]

Hematoporphyrin derivative developed by Beijing Pharmaceutical Industry Research Institute achieved success, gained the extensive application clinically, and accumulated the relatively abundant treatment experience as early as 1980s.[13] In the early of this century, Chongqing Huading Modern

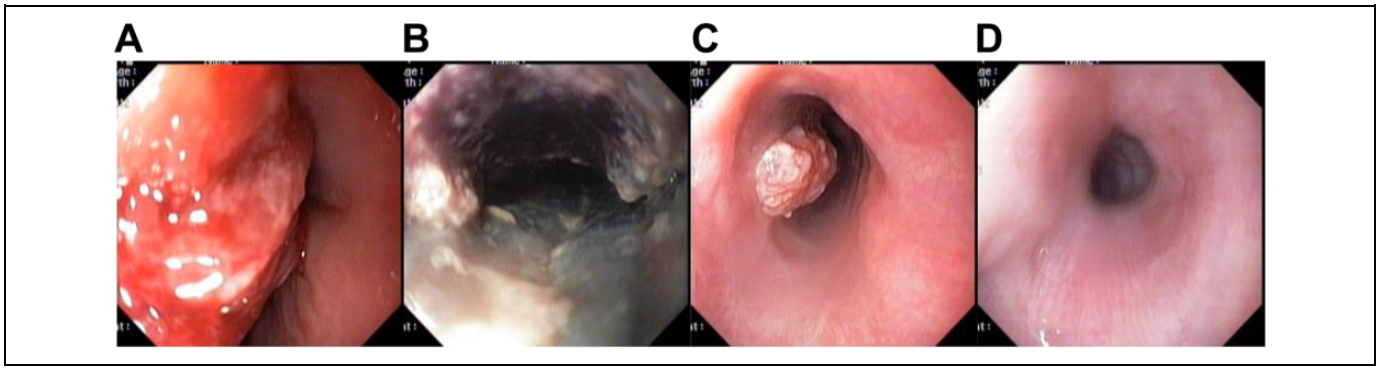

Figure 1. A, Before photodynamic therapy (PDT). Endoscopy shows a protruding mass on the upper esophagus. B, Three days post-PDT. Endoscopy shows coagulation necrosis at the PDT-treated lesion. C, Six weeks post first session of PDT. There was a small residual lesion and the second session of PDT was conducted. D, Six months post second session of PDT, A scar is seen at the previously cancerous lesion and there is no tumor in the biopsied specimens.

Biopharmacy Co, Ltd gained the HpD production technology from Beijing Pharmaceutical Industry Research Institute, developed and produced the Hp injection successfully, reorganized the clinical study and received approval of listing for clinical application.

As the team carrying out PDT earlier in China, we have successively applied HpD and Hp, respectively, coordinate with gold vapor laser and semiconductor laser to treat 79 patients with esophageal cancer during different periods of time since 1990s, and gained good therapeutic effect. Two groups of patients gained satisfactory therapeutic effect, with the effective rate up to about 70%, while the disease control rate (CR + PR + MR) was up to about 90%. Most patients could gain good palliative therapeutic effect, and even some patients at the early stage could reach the radical effect, with favorable compliance and tolerance.

Some patients have the obvious epigastric and (or) retrosternal discomfort or pain related to local tumor necrosis. With the response subsiding, the pain is relieved gradually. The severe pain can be treated by analgesic agents, and mostly the pain is relieved in a few days. Some patients, especially the patients with larger tumor load, who have the obvious local necrosis after PDT, may have a fever and temperature returned to below 38.5°C in 12 hours after treatment, and to normal after conventional treatment, so it is neither necessary nor recommended to use antibiotic therapy clinically.

In general, 2 photosensitizers perform well in terms of therapeutic effects and adverse effects, and the significant difference is not discovered by comparison in between each other, indicating that they have good continuity and inheritance.

However, they belong to the first generation of photosensitizers, with complex component and long retention time in the skin; and patients should stay out of the sun for about 4 weeks. Many patients have the situations of darkening and blackening skin during a longer period of time after treatment, which perplexes some patients and especially female patients.[19]

In China, many new type photosensitizers have entered into different stages of clinical study recently, and 2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a (HPPH) stage I clinical study from our team has been completed with satisfactory preliminary results. The other domestic new type photosensitizer photocyanine has entered stage II clinical trial. Also other studies on the second generation of photosensitizers are developing actively. We believe that various photosensitizers with different function features could be selected and applied clinically in the near future.[20,21]

Declaration of Conflicting Interests

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