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A case of Photodynamic Therapy for Advanced Adenocarcinoma of Esophagogastric Junction

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Abstract: Photodynamic therapy (PDT) is a new minimally invasive technique for the treatment of tumors. Compared with traditional treatments such as surgery, radiotherapy and chemotherapy, PDT has the advantages of targeted killing of primary and recurrent tumor cells, less damage to surrounding normal tissue, less complications and high repetition rate. The purpose of this study was to investigate the short-term efficacy and adverse reactions of photodynamic therapy in advanced elderly patients with esophageal-gastric junction adenocarcinoma without surgical indications. A patient with advanced adenocarcinoma of esophagus and fundus was treated with photodynamic therapy under gastroscope. Intravenous drip of Cipofen (hematoporphyrin injection 150mg/0.9% saline 250ml) for 1 hour to keep the patient away from light.48 hours after administration, photodynamic therapy was performed with "Leimai" PDT630-A photodynamic therapy apparatus, 3cm columnar optical fiber, laser treatment wavelength of 630nm, transmission efficiency of 0.70, output power of 1.4W, irradiation at the lower segment of the esophagus and cardia for 150s. The curative effect was evaluated by comparing gastroscopy before and after photodynamic therapy. Before treatment, there were proliferative lesions in the lower part of esophagus and cardia, erosion and necrosis on the surface, stricture of esophageal cavity, huge ulcer near gastric fundus, filthy moss and dam-like hyperplasia and eminence of surrounding mucosa. After treatment, the local mucosa at the entrance of cardia became white and there was no bleeding. Within four days after treatment, the symptoms of nausea and vomiting disappeared; the adverse reaction of retrosternal discomfort began to occur on the second day after operation, and the adverse reaction was not improved after photodynamic therapy. Photodynamic therapy has a significant short-term effect on advanced elderly patients with adenocarcinoma of the esophagogastric junction, which can significantly alleviate the clinical symptoms and relieve the pain of the patients. However, the adverse reactions can not be ignored. Therefore, photodynamic targeting therapy for tumor needs to be further studied. It is believed that with the continuous development of high-performance photosensitizers and new generation lasers, and the continuous progress of endoscopy and image guidance technology, photodynamic therapy will become an important adjuvant or palliative treatment for tumor prevention and treatment.

Keywords: Photodynamic therapy; Gastric cancer; Adenocarcinoma of esophagogastric junction; Short-term efficacy; Adverse reactions; Hippofen

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1 Introduction

Gastric cancer is one of the most common malignant tumors in China. Its morbidity and mortality ranks first among digestive tract malignant tumors and ranks second among all cancers. Early diagnosis of gastric cancer is difficult, and most cases are in the middle and advanced stage at the time of diagnosis, while the 5-year survival rate of patients with advanced gastric

cancer treated with radical resection is only 20% to 30%. In addition, as an adjuvant therapy, radiotherapy and chemotherapy are often used, but the effect is not ideal, and the side effect is large. In recent years, with the continuous development of photodynamic therapy technology, coupled with its unique advantages such as less trauma, low side effects, repeatable treatment, cooperative surgical treatment, eliminating recessive cancer lesions and protecting the function of important organs from damage, it provides a new model for palliative treatment for patients with advanced cancer. A case of advanced esophageal-gastric junction adenocarcinoma treated with photodynamic therapy was reported, and the influencing factors, short-term efficacy and adverse reactions were discussed.

The patient was 84 years old man. He was admitted to hospital on 20th August in 2019 because of "choking feeling of eating in January". The gastroscope of Rifeng City people's Hospital diagnosed malignant tumor of cardia and fundus of stomach. Blood routine after admission: HB77 g/L, pathological examination showed that 6 tissues (cardia and gastric fundus) were grayish white, ranging from 0.2 × 0.1 × 0.1 cm to 0.1 × 0.05 × 0.05 cm. The pathological diagnosis (Figure 1) is poorly differentiated adenocarcinoma, some signet ring cell carcinoma and some poorly differentiated tubular adenocarcinoma. The patient had advanced tumor, advanced age, long-term anemia, poor cardiopulmonary function and poor nutritional status. The family members of the patient refused operation, radiotherapy and chemotherapy and agreed to photodynamic therapy.

On one day of August 2019, intradermal injection of hematoporphyrin injection (Hippofen) 0.1 ml was given 15 minutes after local allergic reactions such as redness, swelling and other allergic reactions. Hippofen (hematoporphyrin injection 150mg 0.9% normal saline 250ml) was given intravenous drip within 1 hour to keep the patient away from light, and there was no itching, erythema and other discomfort on the patient's skin during the period. On the day of August 2019, intradermal injection of hematoporphyrin injection (Hippofen) 0.1 ml was given 15 minutes after local allergic reactions such as redness, swelling and other allergic reactions. Hippofen was given intravenous drip within 1 hour to keep the patient away from light, and there was no itching, erythema and other discomfort on the patient's skin during the period. Using the PDT630-A photodynamic therapy apparatus of "Leimai" company, using 3cm columnar optical fiber, light source wavelength 630nm, transmission efficiency 0.70, setting output power 2W, measured output power 1.4W, irradiating once at the lower segment of esophagus and cardiac door for 150s, the local mucosa at the entrance of cardia became white and no bleeding was found. The patient was in stable condition during and after operation and returned to the ward safely. On the 25th, the patient was stable and conscious, and there was no obvious discomfort such as nausea and vomiting. On the 26th, the patient complained of retrosternal discomfort, and no obvious discomfort such as nausea and vomiting, and was treated with photodynamic therapy again, the method is the same as above. On the 27th, the patient still complained of retrosternal discomfort, mild tenderness in the upper abdomen, no obvious discomfort such as nausea and vomiting. On the 28th, the patient still reported retrosternal discomfort, and mild nausea and vomiting after eating. On the 29th, the patient still had retrosternal discomfort, and obvious nausea and vomiting after eating fluid. The patient and his family members were required to be discharged from the hospital. During the follow-up, the family member complained that the patient died on the day in September.

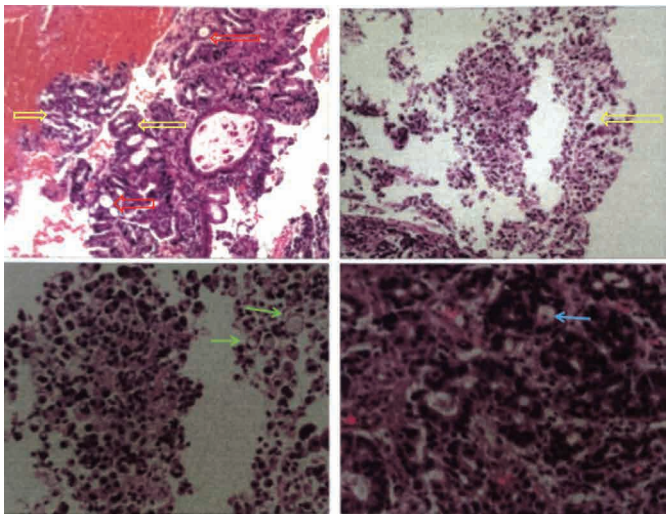
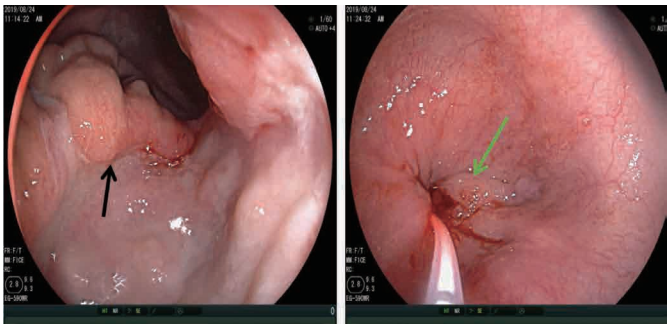


Figure 1. Results of endoscopic pathological examination before treatment.

Pathological diagnosis: (cardia and gastric fundus) poorly differentiated adenocarcinoma (red arrow indicates poorly differentiated, yellow arrow indicates adenoid structure), the part is signet ring

cell carcinoma (green arrow), the part is poorly differentiated tubular adenocarcinoma (blue arrow). Immunohistochemical results: C-erbB-2 (0), Ki67 (80% +).



A B

Figure 2. The results under gastroscope before treatment

Before treatment, there were proliferative lesions in the lower esophagus and cardia, with erosion and necrosis on the surface, esophageal stenosis (green arrow in B), endoscopic passage, huge ulcers in the fundus of stomach near the cardia (indicated by the black arrow in A), covered with filthy moss, and dike-like hyperplasia and eminence of the surrounding mucosa.

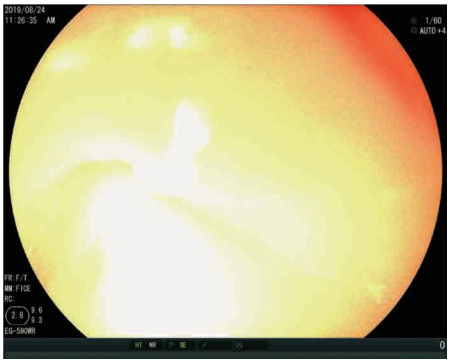


Figure 3. Gastroscopic findings during photodynamic therapy

Irradiate the lower part of the esophagus and the door of the cardia once for 150 seconds.

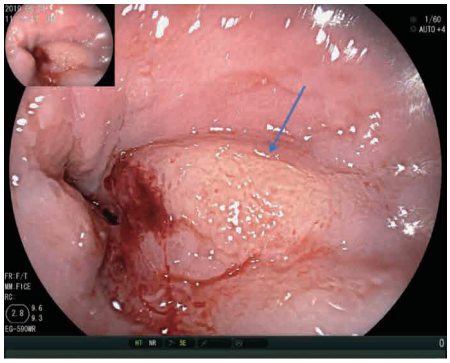


Figure 4. Gastroscopic findings after photodynamic therapy.

The local mucosa at the door of the cardia turned white (pointed to by the blue arrow), and no more bleeding.

Figure 5. Gastroscopic findings on the second day after treatment.

White necrotic material at the door of the heart (indicated by the yellow arrow)

2 Discussion

Photodynamic therapy is a new method for the treatment of tumors developed in the 1970s, which has the advantages of safety, effectiveness, less trauma and high repeatability. Therefore, it has a special position in tumor treatment[2]. The action mechanism of PDT is that under the excitation of external light source, the photosensitizer absorbs light energy from the ground state to the singlet excited state, and then jumps to the triple excited state. The photosensitizer in the triple excited state can have electron transfer or energy transfer with the surrounding biomolecules or oxygen to produce free radicals or reactive oxygen species (ROS) that can damage biomolecules such as proteins and nucleic acids, thus giving full play to their therapeutic activity. It can be seen that photosensitizer, light source and oxygen are the three core elements of PDT[3]. In addition, the individual difference of patients is also another important reason that affects the curative effect. Then it is discussed from the aspects of influencing factors, short-term efficacy, adverse reactions and individual differences.

3 Influencing Factors

3.1 Photosensitizer

The photosensitizer used for photodynamic therapy in this patient is Hippofen, which is divided into the first generation of photosensitizer, which is the only new generation of hematoporphyrin derivative approved for clinical application in the treatment of multiple tumors in the world. Hippofen has a special affinity for tumor tissue, the concentration in tumor tissue

is 10-30 times that of normal tissue at 48 h, and the tumor parenchyma is more than 5 times larger than tumor stroma, but the excretion of tumor tissue is 48-72 hours longer than that of normal tissue, even more than 240 hours. This provides favorable conditions for photodynamic therapy of tumor. Its positive effect can be explained by the curative effect of the patients three days after the end of treatment. Its disadvantage is that the stability of photodynamic damage intensity is poor, the lighting time is long, the time of avoiding light is long, and the skin photosensitive reaction is serious. In addition, because this kind of photosensitizer can not absorb red light well, the treatment depth is not enough, which affects the effect of photodynamic therapy for gastric cancer [1]. It is speculated whether the symptoms improved only in the first three days due to the lack of depth of Hippofen treatment. Therefore, looking for other photosensitizers with more efficient and less toxic side effects is also a direction of current research. Shi found that photosensitized curcumin has significant growth inhibition and apoptosis-increasing effects on human breast cancer MCF-7 cells and human gastric cancer BGC-823 cells, which provides a theoretical basis for the development of curcumin as a photosensitizer for the treatment of gastric cancer.

3.2 Light Source

Light source is also one of the important factors of PDT therapy. It is speculated whether it is difficult to irradiate the huge ulcer surface with cylindrical optical fiber because of the limited penetrating ability of the light source to the gastric wall or the lack of irradiation time, which leads to the long-term effect of PDT is not optimistic enough for this patient. Therefore, the study of new and efficient optical materials is also an important breakthrough to promote the development of PDT. With the development of material science and nanotechnology, the upconversion nanomaterials (UCNPs) with the properties of absorbing near infrared light and emitting visible light have made up for this deficiency to some extent and promoted the development of photodynamic therapy. For example, Li[7] coupled photosensitizer dihydroporphine (Chlorine6,Ce6) with pH responsive polymer and self-assembled with UCNPs (NaYF4Yb,Er@CaF2) and surfactant (PluronicF68) to prepare composite nanomaterials. After reaching the weakly acidic environment of the tumor microenvironment, the composite was depolymerized, which restored the activity of the original gathered and quenched Ce6, and realized the PDT excited by 980nm laser. The above studies overcome the defects such as low depth of tissue penetration caused by ultraviolet and visible light irradiation, but the phototoxicity and tissue damage caused by long-term continuous irradiation are inevitable. It limits the further development and application of photodynamic therapy. Therefore, the development of near-infrared absorption photosensitizers and the reduction of phototoxicity and tissue damage caused by continuous irradiation of external light sources are of great significance to promote the development of PDT [3].

3.3 Oxygen

A large number of reactive oxygen free radicals can be produced in the process of photodynamic therapy, and the killing effect of PDT on diseased tissue is mainly based on the production of reactive oxygen species (ROS) [8]. Different types of ROS, can be produced in the process of PDT, in which singlet oxygen ($^1O_2$) is considered to be the key factor in the photodynamic effect. $^1O_2$ plays a role in tumor cells mainly through oxidative damage mediated by electron transfer[9]. Therefore, oxygen is one of the important factors for the activity of PDT. The patient still had retrosternal discomfort after the second PDT, and the nausea and vomiting were obvious after eating fluid. It was considered that because the microenvironment of the tumor was in a state of hypoxia and the patient had long-term anemia, the oxygen content in the tissue was very low, maybe even hypoxia, and inadequate oxygen supply reduced the efficiency of the second PDT, so it did not improve the discomfort symptoms of the patients. Therefore, it is of great significance to find ways to effectively alleviate the hypoxia state of the tumor site to improve the efficacy of PDT.

4 Short-term Curative Effect

Some studies have shown that the short-term effect of photodynamic therapy in the treatment of advanced digestive tract tumors is good, but the long-term effect is not optimistic [10]. In this literature, 148 cases of postoperative advanced digestive tract tumors confirmed by pathology were divided into 3 groups according to the location of the lesions. There were

19 cases of esophageal cancer in group 1, 114 cases of cardiac carcinoma in group 2 and 15 cases of other gastric cancer in group 3. Hematoporphyrin derivative (HpD) 5 mg/kg was injected intravenously to each patient, and the tumor was irradiated by laser within 48-72 hours after administration. The results showed that the obvious effective rate (CR+SR) for short-term symptom improvement was 54.1% (80max 148), including 47.4% (9pm 19) for esophageal cancer, 55.3% (63max 114) for cardiac cancer, and 53.3% (8max 15) for other gastric cancer. All patients were followed up from half a year to 18 years, 147 cases died and 1 case was alive and in continuous follow-up. There were no serious adverse reactions in the three groups. The choking sensation of this patient disappeared three days after treatment, indicating that PDT can effectively improve the short-term efficacy of patients with advanced digestive tract tumors, which is consistent with the above results.

5 Adverse Reaction

Most of the literatures reported that the adverse reactions caused by photodynamic therapy were mild, including skin photosensitivity, acid regurgitation, nausea, pain in the irradiated site and so on. In this patient, the adverse reaction of retrosternal discomfort occurred on the second day after the first photodynamic therapy. By comparing the pictures before and after endoscopy (Fig. 2 to Fig. 5), it was found that the local mucosa at the door of cardia became white after the first PDT, and on the second day, there was necrosis at the door of cardia. Therefore, retrosternal discomfort is caused by tumor necrosis after the first photodynamic therapy.

6 Individual Difference

Some studies have shown that PDT is effective in the treatment of advanced esophagogastric junction tumors in the elderly[10]. The dead patient had poor cardiopulmonary function, moderate anemia, high malignant degree of tumor and poor prognosis. Therefore, the therapeutic effect of PDT on patients with advanced esophagogastric junction tumors cannot be completely denied.

7 Prospect

As a new method for the treatment of digestive system tumors, the curative effect of PDT is worth affirming. For advanced cancer patients without surgical indications, PDT can relieve clinical symptoms, improve quality of life and prolong survival time. However, photodynamic therapy is still in its infancy in the field of precise tumor therapy. The main research direction in this field is to construct a new photodynamic therapy system with good biosafety, strong tumor targeting ability, good curative effect and low side effects, to find suitable combination therapy and to promote the further development of PDT.

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