Therapeutic Applications: Photodynamic Therapy Using Porphyrin Compounds

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Summary

- Photodynamic therapy (PDT) is a localized cancer therapy using a tumor-affinity photosensitive agent and low-power laser irradiation.
- PDT is safe and easy as compared with ablation or thermal coagulation using high-powered lasers.
- The incidence of photosensitivity as an adverse effect of PDT has improved with the introduction of second-generation photosensitizers.
- PDT is expected to become one of the treatment options for various types of cancer in the future.

1 Introduction

As a result of recent advances in endoscopes and optical fibers, optical engineering has been introduced to medical treatment in these years. Photodynamic therapy (PDT) is a promising treatment method that irradiates a tumor with a highly tumor-accumulating photosensitive agent and a laser with a specific wavelength and shows a cell-killing effect only on tumor cells with high drug concentration. It has already been applied clinically in the fields of pulmonary and digestive surgery, neurosurgery, ophthalmology, dermatology, and urology. As described in other chapters, photodynamic diagnosis (PDD), which is a method to diagnose the localization of tumors by irradiating biological tissues with light and detecting the fluorescence generated by photosensitive agents accumulated in tumors, is also being actively studied and applied clinically.

In Japan, PDT using the first-generation porpfimer sodium (Photofrin®, Wyeth) and the second-generation talaporphyn sodium (Laserphyrin®, Meiji Seika Pharma, Tokyo, Japan) as photosensitive agents are currently covered by the social insurance system. Compared with the first-generation porphyrin sodium, the second-generation talaporphyn sodium has the advantage of reducing the duration and degree of light shielding and is likely to be widely used in clinical practice in the future. In this chapter, we focus on PDT therapy using second-generation photosensitive substances, including future prospects.

2 What Is PDT?

PDT is a therapeutic method in which a photosensitizing tumor-affinity photosensitizer is administered into the body, and the lesion is irradiated with a laser of a specific wavelength to induce a photoreaction that kills the cancer cells. In Japan, PDT with porphyrin sodium is currently covered by insurance for early-stage lung cancer, superficial esophageal cancer, superficial early-stage gastric cancer, early-stage cervical cancer and dysplasia, age-related macular degeneration, and malignant brain tumors, while PDT with thalaborphine sodium is approved for early-stage lung cancer, recurrent esophageal cancer after chemoradiation, and primary malignant brain tumors.

3 Action Mechanism of PDT

Although the mechanism of the cell-killing effect of PDT has not been fully elucidated, it has been shown physicochemically that the PDT effect is caused by a photochemical reaction that occurs when a light-sensitive molecule with a porphyrin skeleton absorbs light energy and transfers this energy to other molecules in the presence of oxygen [1].

Two reactions, radical reaction and singlet oxygen reaction, are induced in photosensitive materials excited by light. The free radicals produced in the radical reaction react with oxygen to produce a variety of oxidants that trigger free radical chain reactions. In the singlet oxygen reaction, the photo-

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sensitive material that receives the laser light energy enters the excited singlet state and supplies energy to the oxygen in the tumor tissue, and the supplied oxygen becomes singlet oxygen. This singlet oxygen is thought to induce necrosis and apoptosis of tumor cells [2]. Recently, tumor blood vessels have also been shown to be a site of PDT injury, causing hemorrhage, hypoxia, and tumor necrosis [3–5]. Furthermore, in addition to the abovementioned direct cell-killing mechanisms by induction of apoptosis and vascular injury by reactive oxygen species, indirect therapeutic mechanisms by oxidative stress after PDT, induction of various cytokines by inflammatory changes, and activation of specific tumor immunity have also been reported [6–8].

Although the laser wavelength depends on the type of photosensitive agents, the optimal absorption wavelength range of sodium porphyrin is 630 nm and that of talaporphyn sodium is 664 nm. After administration, the light-sensitive agent is taken up by the tumor and normal tissues, and the drug concentration increases. Laser irradiation is performed 48–72 hours after intravitreal administration for porfimer sodium and 4–6 hours for talaporphyn sodium. The duration of drug retention in the body is 4–6 weeks and 2 weeks, respectively, which is shorter for talaporphyn sodium. During this time, light shielding is required, and the light shielding level is reduced from less than 300 lux to less than 500 lux with talaporphyn sodium.

4 PDT Treatment in Practice

We will introduce the current practice of PDT using talaporphyn sodium (Laserphyrin®) at our hospital for the recurrence of esophageal cancer after chemoradiotherapy.

PDT is indicated 4–6 hours after intravenous injection of 40 mg/m^2 of Laserphyrin®. For laser excitation, ZH-L5011HJP (PD Laser; Panasonic Healthcare's semiconductor laser, Tokyo Japan) was used with a wavelength set at 664 ± 2 nm. Irradiation was performed with a power density of 150 W/cm^2 and an energy density of 100 J/cm^2 for 11 minutes and 7 seconds at a time. Depending on the lesion, irradiation may be divided into one to three sessions. The PDT laser fiber used in this procedure is classified into two types: a lateral full-field irradiation type and an anterior irradiation type.

After intravenous administration of Laserphyrin®, the patient is shielded from light by a dark curtain around the patient below 500 lux for 14 days. Patients are instructed to stay out of direct sunlight for 2 weeks after discharge and to avoid skin exposure as much as possible when going out during the day.

5 PDT Using First-Generation Porphyrin Sodium

First-generation porphyrin sodium PDT is covered by insurance for early-stage lung cancer, superficial esophageal cancer, superficial early-stage gastric cancer, early-stage cervical cancer and dysplasia, and malignant brain tumors. As mentioned above, however, a light-shielding period of about 4–6 weeks is required, and the frequency of skin toxicity due to photosensitivity is as high as 20–40%. The eximer dye laser system is also very expensive and large, so there are many problems in terms of economic efficiency and simplicity for this treatment to be used widely. In addition, companies have recently announced that they will discontinue maintenance, so the number of facilities where porphyrin sodium PDT can be performed is currently limited even in Japan.

In the field of gynecology, early cervical cancer and dysplasia have been targeted for PDT treatment. Sakamoto et al. compared PDT with conical resection, a uterus-sparing treatment for early cervical cancer and dysplasia, and reported that PDT has a similar cure rate of cervical lesions but a higher possibility of fertility preservation [9].

In the treatment for early-stage gastric cancer, PDT for superficial lesions was covered by the Japanese insurance system in April 1996. While there have been some reports on the efficacy of PDT for early-stage gastric cancer [10], this strategy has not become widespread due to the development and widespread use of EMR (endoscopic mucosal resection) and ESD (endoscopic submucosal dissection).

6 PDT Using Second-Generation Thalaborphine Sodium

Second-generation thalaborphine sodium PDT is covered by insurance for early-stage lung cancer, recurrence of esophageal cancer following chemoradiotherapy, and primary malignant brain tumors in Japan. The indications for each are shown in Table 33.1.

Table 33.1 Indications of PDT using thalaborphine sodium

Indications	Recurrent esophageal cancer chemoradiotherapy	Central early-stage lung cancer	Malignant brain tumor
Selection criteria	Local remnant or recurrent esophageal cancer after CRT or RT	Stage 0 or stage I early-stage lung cancer	Primary malignant brain tumor
Adaptation	Curative treatment such as surgical resection or endoscopic treatment is not possible Wall depth does not exceed the intrinsic muscular layer The longitudinal diameter is less than 3 cm, and the circumference is less than 1/2 circumference It does not extend into the cervical esophagus No distant metastasis or lymph node metastasis	The lesion is centrally located above the area bronchus The entire lesion can be seen endoscopically in the bronchial mucosa Tumor diameter less than 10 mm No lymph nodes or distant metastases	Subtotal or greater resection of the tumor body is expected at the time of surgery The site of probable tumor cell infiltration is expected to be visible under an operating microscope and is expected to be a site where laser irradiation is feasible There are no major blood vessels in the normal cerebral circulation in the area to be irradiated with laser light
Taboo	The tumor is at the aorta T4 prior to CRT or RT Hypersensitivity to Rezafirin Current porphyria	Hypersensitivity to Rezafirin Current porphyria	Hypersensitivity to Rezafirin Current porphyria

7 PDT for Central-Type Early-Stage Lung Cancer

The results of PDT for central early-stage lung cancer were reported to be 84.3% CR rate and 84.6% CR rate in a phase II clinical trial using first-generation porfimer sodium and second-generation talaporphyn sodium, respectively [11, 12]. The response rates were 94.9% and 94.9%, respectively. In particular, CR was reported to be more than 90% when the lesion diameter was less than 10 mm, while it decreased to 50–80% in patients with lesions between 10 and 20 mm. Recently, however, the CR rate of PDT for the lesions with a larger diameter of 10–20 mm and classified as flat, early polypoid, or nodular lesions by endoscopic examinations has been improved to 90.4%, which was higher than previously reported [13]. This may be due to the improved localization diagnosis of central early-stage lung cancer lesions, enabling accurate diagnosis of the area of laser irradiation.

8 PDT for Recurrence of Esophageal Cancer after Chemoradiotherapy

A phase II study using first-generation porfimer sodium for the treatment of recurrent esophageal cancer revealed satisfactory overall outcomes: the CR rate of the primary tumor was 76%, and the 3-year survival rate was 38% [14]. In a phase II clinical trial using second-generation talaporphyn sodium, the CR rate was 88.5%, and local progression-free survival was 428 days, with no serious adverse events, suggesting a high safety profile [15]. Based on these results, PDT for recurrence of esophageal cancer after chemoradiotherapy using talaporphyn sodium was included in the Japanese insurance coverage in October 2015.

After the approval by the Japanese FDA, Amanuma et al. reported that the local complete response rate was 53.6% (60% in patients with pre-PDT depth of T1b and 37.5% in patients with T2 [16]), suggesting that PDT is an effective salvage therapy in clinical practice. In contrast, grade 3 or higher complications occurred in two cases, and grade 5 esophageal bronchopleural fistula occurred in one case, so sufficient caution is required.

9 PDT for Malignant Brain Tumors

Malignant brain tumors, especially glioblastoma, rarely have distant metastasis, and local treatment is important to improve prognosis. In recent years, there have been many reports that aggressive removal is associated with a better prognosis, and in the case of glioblastoma, removal of more than 98% of the contrast-enhancing area on MRI images improves long-term outcomes. The current consensus on the treatment of malignant brain tumors is to aim for maximum removal with minimal neurological complications. Photodynamic diagnosis (PDD) is a method to visualize tumors with obscure borders by the naked eye, and PDT is a therapeutic option offering laser eradication of invasive tumor cells that cannot be removed by surgery.

According to the results of the investigator-initiated clinical trial of talaporphyn sodium PDT started in 2009, the 12-month overall survival rate was 95.5%, and the 6-month progression-free relapse rate was 90.9% [17]. The median overall survival was 24.8 months, and based on the results in

a situation where there are few prospective clinical trials with overall survival exceeding 2 years, thalaborphine sodium PDT is expected to be effective as an add-on to standard therapy and was approved by the pharmaceutical affairs bodies in Japan in 2013. Currently, post-marketing surveillance and clinical studies are underway.

10 PDT Using 5-ALA

5-ALA is metabolized into the fluorescent substance porphyrin IX after intracellular uptake and accumulates more in tumor cells, thus labeling only cells. Therefore, 5-ALA can be used for PDD, especially in the field of neurosurgery. Although PDT targeting 5-ALA has not been approved in Japan, many basic experiments of PDT using 5-ALA for brain tumors such as glioblastoma have been reported worldwide. Depending on the outcomes of current clinical trials, further development of this treatment strategy can be expected [18, 19].

11 PDT for Other Cancers (Especially with Regard to Bile Duct Cancer)

Cholangiocarcinoma arising from the epithelium of the bile duct is one of the cancer types with a poor prognosis, with a 5-year survival rate of about 10%. Surgical curative resection of cholangiocarcinoma is expected to have the best prognosis, but more than half of patients with cholangiocarcinoma are inoperable at the time of detection, and the presence or absence of local control, including bile duct stenosis, has a significant impact on the patient's prognosis. In recent years, the number of reported cases of PDT for the palliative treatment of cholangiocarcinoma has been increasing [20, 21].

Ortner et al. reported that porphyrin sodium PDT combined with biliary stent significantly prolonged survival compared with stent alone in a multicenter randomized trial for unresectable cholangiocarcinoma [22]. In a phase II clinical study, Berr et al. reported that PDT was effective in 23 patients with unresectable cholangiocarcinoma, with tumor reduction in 29–74% of patients, a 6-month survival rate of 74% after PDT, a median survival time of 11 months, no bile stasis, and improvement in QOL [23]. In a cellular-level study, Nonaka et al. reported that the combination of gemcitabine, oxaliplatin, and thalaborphine sodium PDT induced the strongest necrosis and apoptosis in cholangiocarcinoma cells [24]. The usefulness of PDT as a local treatment for cholangiocarcinoma has been almost confirmed, and it is expected that PDT will be widely used in clinical practice through large-scale clinical trials aiming at insurance coverage in the future. We have been conducting a clinical trial on the safety of PDT as a local adjuvant therapy for unresectable cholangiocarcinoma since 2017 under the approval of the hospital ethics committee. Clinical applications of PDT are highly expected also in the field of urological cancer and head and neck cancer [25, 26].

12 Future Perspectives

PDT is a minimally invasive cancer treatment method that takes function preservation into consideration, and it is one of the most promising treatments for elderly patients. In order to develop PDT as a more feasible option for cancer treatment in various fields, a new third-generation photosensitive agent with higher therapeutic efficacy, shorter light shielding period, and fewer side effects is required, as being developed actively in these years [27, 28]. Recently, a water-soluble porphyrin compound synthesized by the porphyrin complex derivatization method developed by Matsumoto et al. has been shown in basic research to have high water solubility, high biocompatibility, high quantum yield of cytotoxic singlet oxygen generation, and higher antitumor effect than Laserphyrin [29]. At our institution, we are currently confirming the efficacy of PDT using this new photosensitizer in basic research.

We hope that PDT will be one of the new methods of cancer treatment in addition to surgery, radiotherapy, and chemotherapy, leading to the improvement of prognosis in cancer patients.

Point

- PDT is a localized cancer therapy using a tumor-affinity photosensitive agent and low-power laser irradiation and has been applied clinically to the recurrence of esophageal cancer after chemoradiotherapy, central early-stage lung cancer, and malignant brain tumors.
- PDT is expected to be applied to various types of malignancies including unresectable cholangiocarcinoma.

References

1. Hilf R, Warne NW, Smail DB, et al. Photodynamic inactivation of selected intracellular enzymes by hematoporphyrin derivatives and their relationship to tumor cell viability in vitro. Cancer Lett. 1984;24:165–72.
2. Weishaupt KR, Gomer CJ, Dougherty TJ. Identification of singlet oxygen as a cytotoxic agent in the photoinactivation of a murine tumor. Cancer Res. 1976;36:2326–9.
3. Fingar VH, Siegel KA, Wieman TJ, et al. The effects of thromboxane inhibitors on the microvascular and tumor response to photodynamic therapy. Photochem Photochem Photobiol. 1993;58:393–9.
4. McMahon KS, Wieman TJ, Moore PH, et al. Effects of photodynamic therapy using mono-L-aspartyl chlorin e6 on vessel constriction, vessel leakage, and tumor response. Cancer Res. 1994;54:5374–9.

5. Gilissen MJ, van de Merbel-de Wit LE, Star WM, et al. Effect of photodynamic therapy on the endothelium-dependent relaxation of isolated rat aortas. Cancer Res. 1993;53:2548–52.
6. de Vree WJ, Essers MC, Koster JF, et al. Role of interleukin 1 and granulocyte colony-stimulating factor in Photofrin-based photodynamic therapy of rat rhabdomyosarcoma tumors. Cancer Res. 1997;57:2555–8.
7. Evans S, Matthews W, Perry R, et al. Effect of photodynamic therapy on tumor necrosis factor production by murine macrophages. J Natl Cancer Inst. 1990;82:34–9.
8. Korbelik M. Induction of tumor immunity by photodynamic therapy. J Clin Laser Med Surg. 1996;14:329–34.
9. Nanashima A, Nagayasu T. Current status of photodynamic therapy in digestive tract carcinoma in Japan. Int J Mol Sci. 2015;33:117–21.
10. Shimoyama Y, Kuribayashi S, Hosaka H, et al. Indications for gastric cancer PDT and the possibility of expanding the indications. J Res Med. 2015;16:3434–40.
11. Furuse K, Fukuoka M, Kato H, et al. A prospective phase II study on photodynamic therapy with Photofrin II for centrally located early-stage lung cancer. The Japan Lung Cancer Photodynamic Therapy Study Group. J Clin Oncol. 1993;11:1852–7.
12. Kato H, Furukawa K, Sato M, et al. Phase II clinical study of photodynamic therapy using mono-L-aspartyl chlorin e6 and diode laser for early superficial squamous cell carcinoma of the lung. Lung Cancer. 2003;42:103–11.
13. Usuda J, Ichinose S, Ishizumi T, et al. Outcome of photodynamic therapy using NPe6 for bronchogenic carcinomas in central airways >1.0 cm in diameter. Clin Cancer Res. 2010;16:2198–204.
14. Yano T, Muto M, Minashi K, et al. Photodynamic therapy as salvage treatment for local failure after chemoradiotherapy in patients with esophageal. Int J Cancer. 2012;131:1228–34.
15. Yano T, Kasai H, Horimatsu T, et al. A multicenter phase II study of salvage photodynamic therapy using talaporfin sodium (ME2906) and a diode laser (PNL6405EPG) for local failure after chemoradiotherapy or radiotherapy for esophageal cancer. Oncotarget. 2017;8:22135–44.
16. Amanuma Y, Horimatsu T, Ohashi S, et al. Association of local complete response with prognosis after salvage photodynamic therapy for esophageal squamous cell carcinoma. Dige Endosc. 2021;33:355–63.
17. Muragaki Y, Akimoto J, Maruyama T, et al. Phase II clinical study on intraoperative photodynamic therapy with talaporfin sodium and semiconductor laser. J Neurosurg. 2013;119:845–52.
18. Stepp H, Beck T, Pongratz T, et al. ALA and malignant glioma: fluorescence-guided resection and photodynamic treatment. J Environ Pathol Toxicol Oncol. 2007;26:157–64.
19. Tetard MC, Vermandel M, Mordon S, et al. Experimental use of photodynamic therapy in high grade gliomas: a review focused on 5-aminolevulinic acid. Photodiagn Photodyn Ther. 2014;11:319–30.
20. Nanashima A, Abo T, Nonaka T, et al. Photodynamic therapy using talaporfin sodium (Leserphyrin®) for bile ductcarcinoma: a preliminary clinical trial. Anticancer Res. 2012;32:4931–8.
21. Suzuki S, Inaba K, Yokoi Y, et al. Photodynamic therapy for malignant biliary obstruction: a case series. Endoscopy. 2004;36:83–7.
22. Ortner ME, Caca K, Berr F, et al. Successful photodynamic therapy for nonresectable cholangiocarcinoma: a randomized prospective study. Gastroenterology. 2003;125:1355–63.
23. Berr F, Wiedmann M, Tannapfel A, et al. Photodynamic therapy for advanced bile duct cancer: evidence for improved palliation and extended survival. Hepatology. 2000;31:291–8.
24. Nonaka Y, Nanashima A, Nonaka T, et al. Synergic effect of photodynamic therapy using talaporfin sodium with conventional anticancer chemotherapy for the. J Surg Res. 2013;181:234–41.
25. Ramsay D, Stevenson H, Jerjes W. From basic mechanisms to clinical research: photodynamic therapy applications in head and neck malignancies and vascular anomalies. J Clin Med. 2021. https://doi.org/10.3390/jcm10194404.
26. Bozzini G, Colin P, Betrouni N, et al. Photodynamic therapy in urology: what can we do now and where are we heading? Photodiagn Photodyn Ther. 2012;9:261–73.
27. Vrouenraets MB, Visser GW, Loup C, et al. Targeting of a hydrophilic photosensitizer by use of internalizing monoclonal antibodies: a new possibility for use in photodynamic therapy. Int J Cancer. 2000;88:108–14.
28. Tanaka M, Kataoka H, Yano S, et al. Antitumor effects in gastrointestinal stromal tumors using photodynamic therapy with a novel glucose-conjugated chlorin. Mol Cancer Ther. 2014;13:767–75.
29. Matsumoto J, Suzuki K, Yasuda M, et al. Photodynamic therapy of human biliary cancer cell line using a combination of phosphorus porphyrins and light emitting diode. Med Chem. 2017;25:6536–41.