Photodiagnosis and Photodynamic Therapy 25 (2019) 29–34

Contents lists available at ScienceDirect

Photodiagnosis and Photodynamic Therapy

journal homepage: www.elsevier.com/locate/pdpdt

Photodynamic therapy with talaporfin sodium induces dose- and time-dependent apoptotic cell death in malignant meningioma HKBMM cells

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ARTICLE INFO

Keywords:
Photodynamic therapy
Talaporfin sodium (NPe6)
Malignant meningioma
HKBMM cells
Apoptosis

ABSTRACT

Objective: To investigate the effect of photodynamic therapy (PDT) with the talaporfin sodium (mono-L-aspartyl chlorine e6: NPe-6) on human malignant meningioma cell line HKBMM cells in vitro.
Material and methods: After incubation with NPe6 for 4 h, cells underwent PDT (diode laser irradiation: 3.4 mW/cm^2 and 1 J/cm^2. Cell viability was determined in 2 malignant meningioma cell lines (human origin; HKBMM cells and rat origin; KMY-J cells) and human malignant glioma U251 cells with Cell Counting Kit-8 assay. The HKBMM cells were examined for caspase-3 activity, annexin V or propidium iodide (PI) staining, and lactate dehydrogenase leakage. Morphological change was also investigated with phase-contrast microscopy.
Results: In human malignant meningioma HKBMM cells, viability showed a dose- and time-dependent decrease. After 24 h of laser irradiation, NPe6 at 20 μg/ml or more induced a significant decrease in cell viability in both HKBMM cells and KMY-J cells, although they more resistance than the malignant glioma cell line U251 cells. Two kinds of morphological change were also observed in the HKBMM cells, shrinkage of the cell body, indicating apoptosis, and swelling of the cell body, indicating necrosis. In addition, both caspase-3 activity and DNA fragmentation, biochemical markers indicative of apoptosis, showed a dose-dependent increase. The percentage of necrotic cells showing positive staining for annexin V or PI was greater than that of apoptotic cells at a high concentration of NPe6. Lactate dehydrogenase leakage, a biochemical marker of necrosis, also showed a marked increase at a high concentration of NPe6.
Conclusion: Photodynamic therapy with NPe6 induced dose- and time-dependent apoptosis in human malignant meningioma HKBMM cells. At a high concentration of NPe6, however, it induced necrosis.

1. Introduction

Photodynamic therapy (PDT) is a treatment modality in which a photosensitizer (PS) accumulated into tumor tissue or a neo-vascular lesion, is irradiated with a laser at a specific wavelength. This causes a photochemical reaction in the PS which produces singlet oxygen (a reactive oxygen species ROS), resulting in degenerative necrosis of the target cells.

The prognosis for glioblastoma remains poor, with no improvement being seen over the last two decades, and the standard treatment yields median survival of only 18 months [1]. The difficulty in treating and improving the prognosis for malignant gliomas arise from the invasiveness of the tumor cells and protection of the local cerebral function.

Studies using glioblastoma cell lines have demonstrated that PDT using the second-generation PS, talaporfin sodium (mono-L-asparthyl chlorine e6: NPe6) induces mitochondrial apoptotic cell death accompanied by tumor necrosis [2–5]. In a Phase II clinical study on intraoperative PDT with NPe6 and a semi-conductor laser in patients with malignant glioma, it leads to a positive impact was observed on overall survival and local control [6].

Meningiomas are the most common type of primary intracranial tumors. The majority are histologically benign, but less than 3% of meningiomas are malignant (also termed anaplastic or WHO grade III). This latter type is an aggressive tumors with poorer local control and poorer overall survival than seen with benign meningiomas. Median overall survival in patients with malignant meningiomas has been demonstrated to be less than 2–3 years [7–10]. Even with aggressive management including surgery, radiation therapy and chemotherapy, local control remains difficult to attain [10].

The purpose of the present study was to investigate the effect of PDT

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https://doi.org/10.1016/j.pdpdt.2018.10.022
Received 5 June 2018; Received in revised form 27 October 2018; Accepted 29 October 2018
Available online 31 October 2018
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with NPe6 on human and rat malignant meningioma cell lines (HKBMM and KMY-J cells, respectively). The effect on malignant meningioma cell lines and malignant glioma cell lines was also compared and the precise mechanism underlying cell death by application of PDT in human malignant meningioma HKBMM cells investigated. We believe that PDT might offer a viable alternative to standard therapies in the treatment of malignant meningioma.

2. Materials and methods

2.1. Materials

Talaporfin sodium was provided by Meiji Seika Pharma Co., Ltd. (Tokyo, Japan). The Cell Counting Kit-8 (CCK-8), a commercially available assay kit, and the NucView^{TM} 488 caspase-3 assay kit for live cells were obtained from Dojindo (Kumamoto, Japan) and Biotium, Inc. (Hayward, CA, USA), respectively. The MEBCYTO apoptosis kit (fluorescein isothiocyanate (FITC)-labeled Annexin V [Annexin V-FITC] with propidium iodide [PI] kit) and MEBSTAIN apoptosis TUNEL kit direct were obtained from Medical and Biological Laboratories (Nagoya, Japan). Lactate Dehydrogenase (LDH) Cytotoxicity Assay Kit was obtained from Cayman Chemical Company (Ann Arbor, MI, USA).

2.2. Treatment of HKBMM cells, KMY-J cells and U251 cells with NPe6-PDT

Human malignant meningioma HKBMM cells (RCB0680, Riken Cell Bank, Tsukuba, Japan) were seeded at 1×10^4 cells/well in 96-well plates (Thermo Fisher Scientific, Waltham, MA, USA) in Ham's F12 medium (Thermo Fisher Scientific) supplemented with 15% fetal bovine serum (FBS: Nichirei bioscience, Tokyo, Japan) and incubated at 37°C in a 5% CO_2 atmosphere for 24 h. Rat malignant meningioma KMY-J cells (RCB1753, Riken Cell Bank) were cultured in minimal essential medium (MEM: Thermo Fisher Scientific) supplemented with 10% FBS and human malignant glioma U251 cells (Riken Cell Bank) were cultured in Dulbecco's modified eagle medium (DMEM: Thermo Fisher Scientific) supplemented with 10% FBS. After 24 h incubation for 24 h, these cells were incubated with the NPe6 at a concentration of 0–50 μg/ml for 4 h in fresh culture medium. After 4 h, the cells were washed with Ca^{2+}, Mg^{2+} -free phosphate buffered saline (PBS[-]) and incubated for 1 h in fresh medium. The cells were then subjected to semiconductor laser irradiation (wave length 664 nm, laser power 3.4 mW/cm^2, total amount of irradiation, 1 J/cm^2) using the semiconductor laser irradiator ZH-L5011HJP (Panasonic Healthcare Co., Ltd., Tokyo, Japan).

2.3. Measurement of cell viability

Cell viability was measured with the CCK-8 assay kit at 0, 6,12, 18 or 24 h after PDT treatment. The appropriate amount of CCK-8 solution was added to the culture medium. The cells were then incubated at 37°C for 1 h. After incubation, the reaction was terminated by adding 0.01 M hydrochloric acid to the culture medium. Absorbance was measured at 450 nm (reference wavelength, 600 nm) using an absorbance meter (Varioskan; Thermo Scientific, Tokyo, Japan) in accordance with the manufacturer's instructions. Each experiment was performed in triplicate to ensure the reproducibility of the results. Cell viability was calculated from the ratio of the absorbance of each sample to the mean absorbance (100%) of NPe6-unterated samples. Phase contrast imaging of the cell layers was performed using DMi1 inverted microscopy (Leica Microsystems, Wetzlar, Germany).

2.4. Measurement of caspase-3 activity, DNA fragmentation, and annexin V and PI staining

At 24 h after PDT treatment, floating cells and lightly adhering cells were collected following washing with PBS(-). Adherent cell were detached from the bottom of the culture wells by incubation with trypsin-EDTA solution (Sigma-Aldrich, St. Louis, MO, USA) for 2 min. After incubation, culture medium was added to the culture wells and the cells then collected. Caspase-3 activity, DNA fragmentation, and Annexin V and PI staining were quantified in these collected cells. Caspase-3 activity was determined using the NucView^{TM}488 caspase-3 assay kit for live cells. After treating the cells with appropriate concentrations of caspase-3 assay substrate for 30 min at room temperature in the dark in accordance with the manufacturer's instructions, the cell suspension was diluted with culture medium. The cells were then subjected to fluorescence analysis by flow cytometry (FACSCalibur, Becton-Dickinson, NJ, USA). DNA fragmentation was measured by quantifying the binding of deoxyuridine triphosphate (dUTP) – FITC to the nicked DNA of the cells using the MEBSTAIN Apoptosis Kit Direct in accordance with the manufacturer's instructions. Cells were then subjected to fluorescence analysis by flow cytometry FACSCalibur. Apoptosis and necrosis were distinguished by evaluating the number of cells positively stained for cell surface-exposed phosphoserine (annexin V) and PI. The populations of annexin V-positive and PI-negative cells (apoptotic cells) and annexin V-positive and PI-positive cells (necrotic cells) were determined with the MEBCYTO Apoptosis Kit and flow cytometry. The FITC-signal of annexin V was detected at 530 nm by FL1 (FITC detector) and PI fluorescence was detected at 620 nm by FL2 (phycoerythrin fluorescence detector). Assuming a forward and 90°side scatter, a threshold was set that voided the counting of debris, and a gate set that counted cells but not apoptotic and necrotic bodies.

2.5. LDH leakage assay

At 24 h after PDT treatment, the culture medium was harvested, and an aliquot of the medium was used to measure LDH activity with a LDH cytotoxcity assay kit in accordance with the manufacturer's instructions. Absorbance in each sample was measured at 480 nm (reference wavelength: 680 nm) using the Varioskan absorbance meter.

2.6. Statistical analysis

The statistical significance of the data was determined using an analysis of variance (ANOVA) and the Student's *t*-test or Bonferroni's multiple *t*-test as appropriate. A *P*- value of < 0.05 was considered statistically significant.

3. Results

3.1. NPe6-PDT induces dose- and time-dependent cell death in human malignant meningioma HKBMM cells

In cells treated with NPe6 at a concentration of 15–20 μg/ml, cell viability remained above 60%, even at 24 h. (Fig. 1) On the other hand, viability in cells treated with NPe6 at a concentration of 25–50 μg/ml showed a clear decrease. Meanwhile, viability in cells treated with NPe6 at a concentration of 30–50 μg/ml was below 10% at 24 h. These results indicate that the viability of HKBMM cells treated with ≧ 25 μg/ml NPe6 decreased in a dose- and time-dependent manner. In addition, after laser irradiation, viability in untreated HKBMM cells was 100% (Fig. 1), suggesting that cell death was not induced by laser irradiation alone.

3.2. NPe6-PDT induces cell death in not only HKBMM cells, but also rat meningioma KMY-J cells similarly

The results revealed that sensitivity in rat malignant meningioma KMY-J cells tended to be similar to that in human HKBMM cells with NPe6-PDT treatment. On the other hand, sensitivity to NPe6-PDT differed between malignant meningioma cell lines (HKBMM and KMY-J

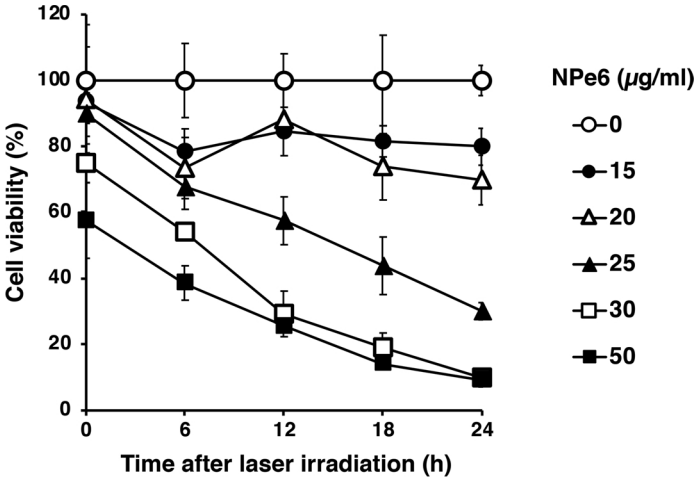

Fig. 1. NPe6-PDT induces dose- and time-dependent cell death in human malignant meningioma cell line.
Human malignant meningioma HKBMM cells were pre-incubated with various NPe6 concentrations (0–50 μg/ml) for 4 h and then subjected to laser irradiation. Cell viability was evaluated after 0, 6, 12, 18, and 24 h. Each value represents the mean ± S.D. from experiments conducted at least in triplicate.

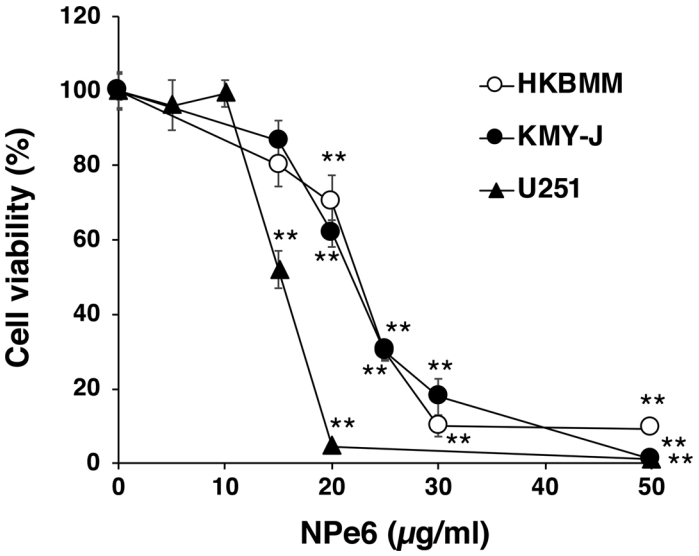

Fig. 2. Effect of NPe6-PDT on human malignant meningioma HKBMM cells, rat malignant meningioma KMY-J cells and human glioma U251 cells.
Human meningioma HKBMM cells, rat malignant meningioma KMY-J cells, and human glioma U251 cells were pre-incubated with NPe6 concentrations (0 ~ 50 μg/ml) for 4 h and then subjected to laser irradiation. Cell viability was evaluated after 24 h. Each value represents the mean ± S.D. from experiments conducted at least in triplicate. Significantly different from the corresponding control, $^{**}P < 0.01$.

cells) and U251 cells (Fig. 2). At 24 h after exposure to 20 μg/ml NPe6-PDT treatment, viability of U251 cells was less than 10%, whereas that in t HKBMM and KMY-J cells was over 50%.

3.3. Morphological change in human malignant meningioma HKBMM cells treated with NPe6-PDT

Fig. 3 shows the morphological observation of NPe6-PDT-treated HKBMM cells. No morphological changes was observed at any time point in cells not treated with NPe6. In cells treated with NPe6 at a concentration of 20 μg/ml, a time-dependent increase was observed in cells showing shrinkage. In cells treated with NPe6 at a concentration of 25 μg/ml, shrinkage was observed from at 6 h onward. At 18 h onward, however, swelling was noted in a few cells. In cells treated with NPe6 at a concentration of 30 μg/ml, both shrinkage and swelling of cells were observed. In cells treated with NPe6 at a concentration of 50 μg/ml, shrinkage and swelling had already appeared at immediately after irradiation (at 0 h). At 12 h onward, a greater increase was observed in swelling cells than in shrinking cells. Cells treated with NPe6-PDT began to exhibit shrinkage and swelling. Shrinking cells showed a dose – and time-dependent increase. At a high dose, swelling occurred, with such cells outnumbering those showing shrinkage.

3.4. Induction of apoptosis and necrosis by NPe6-PDT

As shown in Fig. 4A, DNA fragmentation showed a dose-dependent increase with treatment with NPe6 at concentrations ranging from 20 to 50 μg/ml at 24 h after PDT. An increases in caspase-3 activity was also observed in HKBMM cells treated with 25 or 30 μg/ml NPe6. Nevertheless, the caspase-3 activity showed a decrease at 50 μg/ml NPe6 (Fig. 4B). The population of apoptotic and necrotic cells after NPe6-PDT treatment in HKBMM cells were then evaluated. Apoptosis and necrosis were distinguished by determining the number of cells showing positive staining for annexin V or PI followed by flow cytometry. Annexin V-positive and PI-negaitve cells represented apoptotic cells, while cells positive for both, represented necrotic cells. As shown Fig. 4C, the percentage of apoptotic cells showed a significant increase in HKBMM cells treated with 20–30 μg/ml NPe6-PDT, whereas no such increase was observed in cells treated with 50 μg/ml NPe6. Instead, the percentage of necrotic cells showed a dose-dependent increase (Fig. 4D). Fig. 5 shows the amount of LDH leakage, a biochemical marker of necrosis, from HKBMM cells into conditioned medium after NPe6-PDT treatment. A dose-dependent increase in LDH leakage was observed in the cells. These results showed that NPe6-PDT mainly induced apoptosis with low-dose NPe6 treatment, and that NPe6-PDT mainly induced necrosis at a high dose.

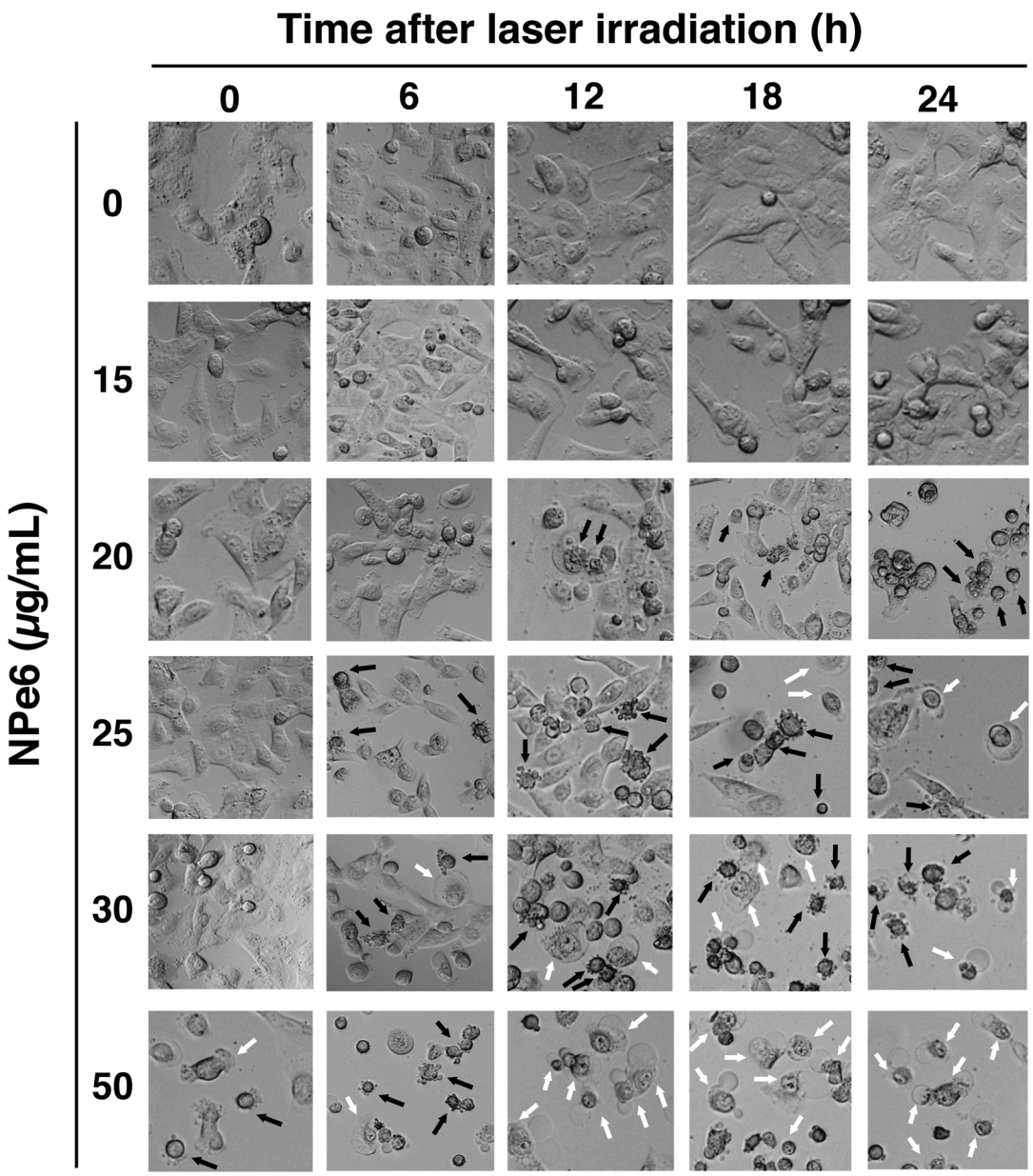

Fig. 3. Morphological changes in human malignant meningioma HKBMM cells after NPe6-PDT.
Human malignant meningioma HKBMM cells were pre-incubated with various NPe6 concentrations (0–50 μg/ml) for 4 h and then subjected to laser irradiation. Cell morphology was evaluated after 0, 6, 12, 18 and 24 h. Black arrows: membrane-blebbing cells, White arrows: swelling cells, original magnification x100.

4. Discussion

Two types of malignant meningioma cell lines were used in the present study. Sensitivity to NPe6-PDT was similar between human malignant meningioma HKBMM cells and rat malignant meningioma KMY-J cells, although human malignant glioma U-251 cells were more sensitive than these malignant meningioma cells. The type of cell death induced by PDT with NPe6 in HKBMM cells was also investigated. At a low concentration of NPe6, Npe6-PDT treatment induced apoptosis, while at a high concentration of NPe6, it induced necrosis. Apoptosis was characterized by shrinkage and blebbing, while necrosis was characterized by rounding of the cells. A gain in cell volume, swelling of organelles and rupture of plasma membrane were also observed morphologically on phase contrast images after NPe6-PDT. In the apoptotic index, both caspase-3 activity and the percentage of apoptotic cells showed a similar decrease in HKBMM cells treated with a high concentration of NPe6. On the other hand, in the necrosis index, both the percentage of necrotic cells and LDH leakage showed an increase in cells treated with a high concentration of NPe6. These results suggested that the main type of cell death changed form apoptosis to necrosis at a high concentration. With a high concentration of NPe6, activation of caspase-3 showed a reduction, while leakage of LDH showed an increase. Fragmentation of DNA, however, which is an indicator of apoptosis showed an increase with a high concentration of NPe6, indicating secondary necrosis. With secondary necrosis, cellular disintegration occur in the absence of scavenger cells. An apoptotic cell maintains cytoplasmic membrane integrity, while molecular alterations, largely due to activated caspases, produce the classical apoptotic phenotype [11–13]. If scavenging capacity is insufficient, however, secondary necrosis may occur here, cytolysis induces a potentially lethal release of cellar components, resulting in karyorrhexis, pyknosis, release of activated caspase-3, cytoplasmic swelling, and lysosomal and cytoplasmic membrane permeabilization [14–16]. At a concentration of 50 μg/ml NPe6, PDT would result in excessive clearance of apoptotic

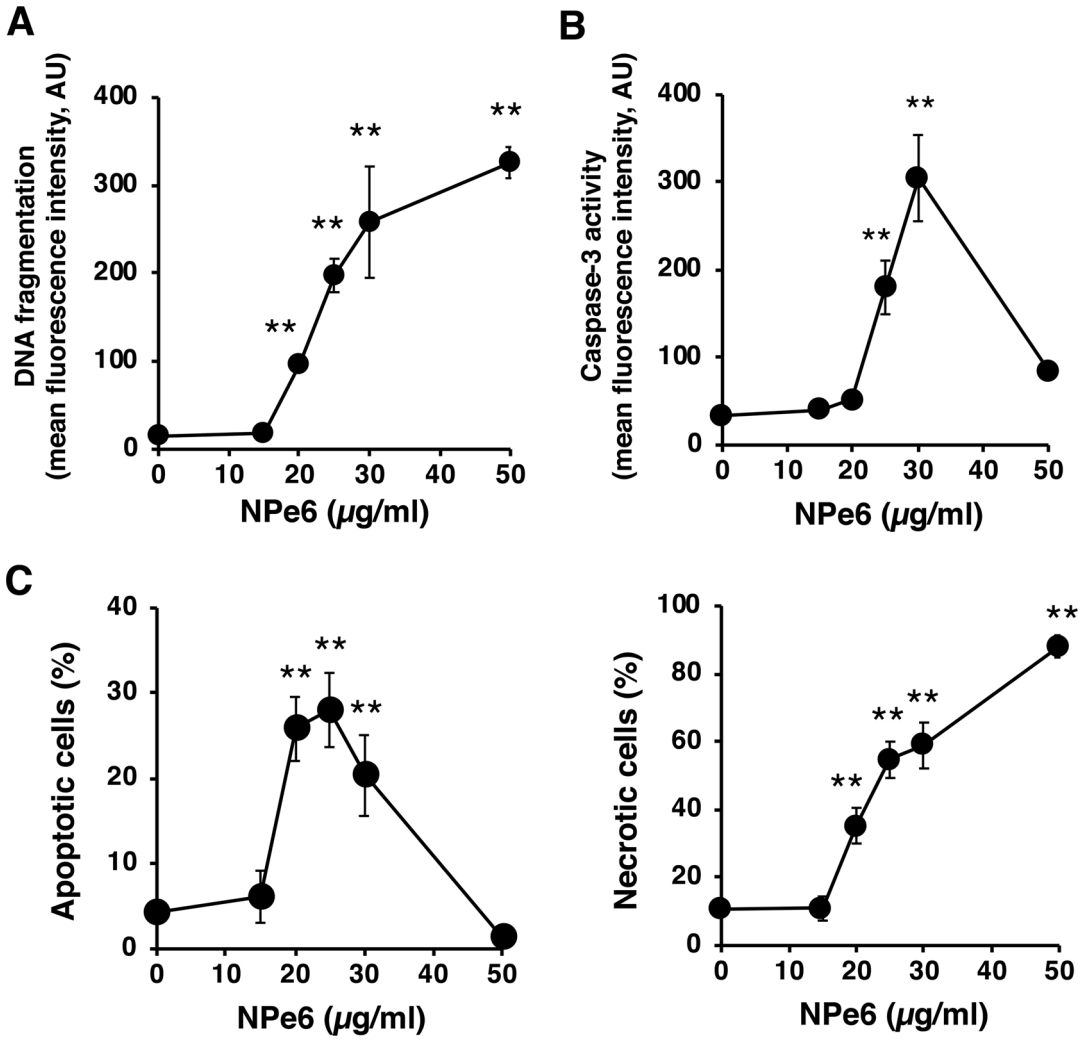

Fig. 4. Effect of NPe6-PDT on two-types of cell death (apoptosis and necrosis) in HKBMM cells.
Human malignant meningioma HKBMM cells were pre-incubated with various NPe6 concentrations (0–50 μg/ml) for 4 h and then subjected to laser irradiation. Indices of apoptosis and necrosis were calculated after measuring fluorescence using flow cytometer at after 24 h incubation. [A] DNA fragmentation, [B] caspase-3 activity, [C] percentage of apoptotic cells (annexin V-positive and PI-negative cells) and [D] percentage of necrotic cells (annexin V-positive and PI-positive cells). Each value represents the mean ± S.D. from experiments conducted at least in triplicate. Significantly different from the corresponding control, $^{**}P < 0.01$.

cells.

The present results also demonstrated that the susceptibility of human malignant meningioma HKBMM cells and rat malignant meningioma KMY-J cells to NPe6-PDT was much lower than that of U251 human glioblastoma cells. The efficacy of PDT is estimated to be dependent on the extent of ROS production in the target tumor cells and on the sensitivity to ROS-induced cytotoxicity. The amount of ROS production is determined by the photochemical reaction induced by PDT, and also depends on the intracellular content of the PS, intracellular oxygen concentration, and excitation laser energy. In the present study, the light dose was set at 1 J/cm^2. This suggests that the difference depends on the intracellular concentration of the PS. The intracellular concentration of PS depends on the preferential uptake and retention. One study reported that ABCG2, an ATP-binding cassette half-transporter, plays an important role as a factor in determining the content of 5-ALA in the tumor cells [17]. Further investigation is needed to clarify the effect of control of intracellular content of NPe6 in PDT.

In the present study, the intracellular oxygen concentration would have been the same, as the cell culture conditions were standardized. PDT involves an oxygen-consuming reaction, which causes hypoxia-mediated destruction of tumor vasculature, resulting in effective treatment. Hypoxia induces up-regulated expression of vascular endothelial growth factor (VEGF), which promotes cell regrowth and vascularization [18].

Xu et al. showed that the expression of VEGF increased after PDT-ZnPcS4-BSA on human U251 glioma cells in vitro [19]. The concentration of VEGF showed an increase after PDT-NPe6 due to hypoxia in a manner dependent on photosensitizer concentration in lung tumor cells in vitro [20]. Difference in expression of VEGF induced by PDT-NPe6 could be relative to PDT-sensitivity. The exact mechanisms underlying this are still not understood, however. Other effects may exist and need further fundamental research.

Preliminary work indicated that meningioma cells were more resistant to 5-aminolevulinic acid (5ALA) or H3-tertraphenylphosphonium (H3-TPP) than glioma cells [21,22]. It was found that protoporphyrin IX (PPIX) did not accumulated in tissues of mesodermal origin [23]. Another study reported that malignant astrocytoma cells showed preferential uptake and retention of H3-TPP relative to benign and malignant meningioma cells and normal controls. Benign and malignant cells behaved similarly for retention but the benign meningioma cells demonstrated a little stronger uptake than the malignant meningioma cells [12]. The percentage cell survivals in 5 subtypes of meningioma cell lines treated with PDT using hematoporphyrin

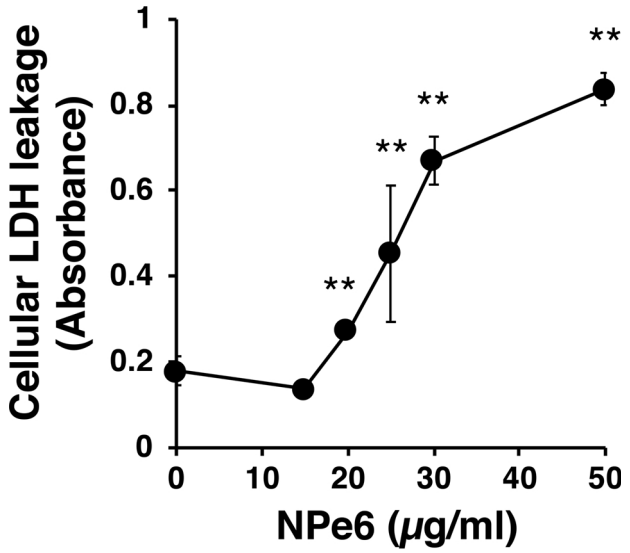

Fig. 5. Induction of necrosis by NPe6-PDT in human malignant meningioma HKBMM cells.
Human malignant meningioma HKBMM cells were pre-incubated with various NPe6 concentrations (0–50 μg/ml) for 4 h and then subjected laser irradiation. LDH leakage from cell into the conditioned medium was evaluated after 24 h. Each value represents the mean ± S.D. from experiments conducted at least in triplicate. Significantly different from the control, $^{**}P < 0.01$.

derivative showed dose-dependent reduction at a fixed power density. These 5 meningioma cell lines comprised 4 benign meningiomas and 1 malignant meningioma (grade II). The survival curves of these benign and malignant meningioma cell lines showed no significant difference [24]. The intracellular concentration of PPIX was much higher in glioma cells than in malignant meningioma [25].

All neurosurgeons try to remove completely the tumor and any adhering dura matter membrane. Complete removal is not possible with some meningiomas, due to involvement of the structures such as the cranial nerves or perforating arteries, or as a

Result of being located in the venous sinus, clivus or petrous apex, which might induce the postoperative neurological deficit, or liquorrhea. Adjuvant radiation therapy is a standard component of initial therapy, but malignant meningioma has a high rate of local recurrence. Some studies have reported that stereotactic radiosurgery (SRS), fractionated external beam radiation therapy (EBRT), protons, photons, or chemotherapy yielded an improvement in the survival rate, but these treatments remains controversial. [26] PDT is useful to control of local failure in case of malignant meningioma. It may be useful to perform NPe6-PDT intraoperatively in dealing with incompletely resected malignant meningioma. Further study is needed to confirm the effect of PDT-NPe6 on malignant meningioma.

5. Conclusion

In human malignant meningioma cell lines, PDT using NPe6 and a diode laser induced cell death dose-dependently and time-dependently. The kinds of cell death comprised apoptosis and necrosis, based on observation of an increase in caspase-3 activity, DNA fragmentation, annexin V and PI staining, and leakage of LDH. Sensitivity to NPe6-PDT in malignant meningioma cells was poorer than that in malignant glioma U251 cells. This ay have been due to differences in the intracellular concentration of NPe6.

Acknowledgements

We would like to thank Dr. Yamate J for providing rat malignant meningioma cell line KMY-J, and also thank Dr. Ishiwata I for providing human malignant meningioma cell line HKBMM. NPe6 was kindly provided by Meiji Seika Pharma Co., Ltd. (Tokyo, Japan). The semiconductor laser device was kindly provided by Panasonic Shikoku Electronics Co. Ltd. (Ehime, Japan). The authors are indebted to Professor Jeremy Williams, Chair of the Department of International Medical Communications at Tokyo Medical University, for editing and reviewing the manuscript.

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