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Modification of extracorporeal photopheresis technology with porphyrin precursors. Comparison between 8-methoxypsoralen and hexaminolevulinate in killing human T-cell lymphoma cell lines in vitro

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ABSTRACT

Background: Extracorporeal photopheresis that exposes isolated white blood cells to 8-methoxypsoralen (8-MOP) and ultraviolet-A (UV-A) light is used for the management of cutaneous T-cell lymphoma and graft-versus-host disease. 8-MOP binds to DNA of both tumor and normal cells, thus increasing the risk of carcinogenesis of normal cells; and also kills both tumor and normal cells with no selectivity after UV-A irradiation. Hexaminolevulinate (HAL)-induced protoporphyrin-IX is a potent photosensitizer that localizes at membranous structures outside of the nucleus of a cell. HAL-mediated photodynamic therapy selectively destroys activated/transformed lymphocytes and induces systemic anti-tumor immunity. The aim of the present study was to explore the possibility of using HAL instead of 8-MOP to kill cells after UV-A exposure.
Methods: Human T-cell lymphoma Jurkat and Karpas 299 cell lines were used to evaluate cell photoinactivation after 8-MOP and/or HAL plus UV-A light with cell proliferation and long term survival assays. The mode of cell death was also analyzed by fluorescence microscopy.
Results: Cell proliferation was decreased by HAL/UV-A, 8-MOP/UV-A or HAL/8-MOP/UV-A. At sufficient doses, the cells were killed by all the regimens; however, the mode of cell death was dependent on the treatment conditions. 8-MOP/UV-A produced apoptotic death exclusively; whereas both apoptosis and necrosis were induced by HAL/UV-A.
Conclusion: 8-MOP can be replaced by HAL to inactivate the Jurkat and Karpas 299 T-cell lymphoma cells after UV-A irradiation via apoptosis and necrosis. This finding may have an impact on improved efficacy of photopheresis.

1. Introduction

Extracorporeal photopheresis (ECP) can be used in the treatment of various immune mediated diseases and has for more than two decades been approved for the treatment of cutaneous T-cell lymphoma (CTCL) and graft-versus-host disease (GvHD) [1]. CTCL represents a heterogenous group of non-Hodgkin's lymphoma; while GvHD is a complication that can occur after stem cell or bone marrow transplantation in which immune cells attack the transplant recipient's body. ECP is a form of apheresis and photodynamic therapy (PDT) where leucocytes (white blood cells) are separated from whole blood and exposed to photoactive 8-methoxypsoralen (8-MOP) as a photosensitizer and ultraviolet-A (UV-A) light before reinfused back to the patient's circulation. In CTCL 8-MOP is thought to bind covalently to DNA in the separated leucocytes resulting in cell cycle arrest and apoptosis. However, risk of the development of cutaneous malignances after the use of psoralens under the conditions of PUVA (psoralen plus UV-A) therapy has been suggested [2]. 8-MOP binds to DNA of not only neoplastic cells, but also normal

Abbreviations: ALA, 5-aminolevulinic acid; CTCL, cutaneous T-cell lymphoma; ECP, extracorporeal photopheresis; FBS, fetal bovine serum; HAL, hexaminolevulinate; GvHD, graft-versus-host disease; MOP, methoxypsoralen; MTS, (4,5.dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium; PDT, photodynamic therapy; PI, propidium iodide; PpIX, protoporphyrin IX; PUVA, psoralen plus ultraviolet-A; UV, ultraviolet

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cells, thus increasing potential risk of carcinogenesis. Moreover, 8-MOP induces cell death to both tumor and normal cells with no selectivity after UV-A light exposure.

Our previous studies have established a biological basis for modification of ECP technology with porphyrin precursors, such as 5-aminolevulinic acid (ALA) or its hexylester (HAL) [3–6]. In the cells, ALA is formed from glycine and succinyl CoA at the beginning of the heme biosynthetic pathway. In the last step of this pathway, iron is incorporated into an intermediate product protoporphyrin IX (PpIX) to form heme. The PpIX is a potent photosensitizer and may accumulate in the cells after administration of exogenous ALA [3,4]. Topically applied ALA is commonly used in PDT of superficial cutaneous malignancies yielding favorable treatment results [3,4]. Since ALA has a hydrophilic character, more lipophilic ALA esters, including HAL, have been developed to penetrate more easily through cellular membranes [7,8]. Success of the clinical application of such esters has been documented. As an example, HAL has been used intravesically for bladder cancer detection with excellent results as shown in a recent meta-analysis [9].

The main advantage of using ALA or HAL for ECP would be that ALA/HAL-induced PpIX as a potent photosensitizer localizes at membranous structures outside of the cell nucleus [3] thus decreasing the risk of potential carcinogenesis as compared to 8-MOP. Moreover, ALA/HAL-induced PpIX after light exposure selectively destroys activated/transformed lymphocytes [10–12]. In addition, PDT can induce systemic anti-tumor immunity (e.g. [13,14]).

In the present study, we have used the human T-cell lymphoma Jurkat and Karpas 299 cell lines as in vitro models of cutaneous T-cell lymphoma to test the possibility of using HAL in combination with UV-A to inactivate the cells. We have also compared the mode of cell death mediated by 8-MOP/UV-A and HAL/UV-A.

2. Materials and methods

2.1. Chemicals

Hexaminolevulinate (HAL) was provided by Photocure ASA (Oslo, Norway). A fresh stock solution of HAL was prepared in a mixture (1:9) of ethanol and serum free RPMI 1640 medium (PAA Laboratories GmbH, Fisher Scientific, Norway) to a concentration of 8 mM before each experiment. The stock solution of 8-methoxypsoralen (8-MOP) was prepared in absolute ethanol and kept in a freezer until use. All the chemicals used were of the highest purity commercially available.

2.2. Cell lines

The human T-cell lymphoma cell lines, Jurkat (ATCC number: TIB-152™) and Karpas 299 (DSMZ, Germany), growing in suspensions, were used in the study. The cells were incubated in RPMI 1640 medium supplemented with 10% fetal bovine serum (FBS, Gibco, Invitrogen, Norway), L-glutamine (Gibco, Invitrogen, Norway), penicillin and streptomycin (Gibco, Invitrogen, Norway). For subcultivation, the cells were diluted to a density of 3×10^5 cells/ml every second day. For experiments, the cells were diluted to a density of 1×10^6 cells/ml the day before the start of experiment.

2.3. Fluorescence spectroscopy

Fluorescence excitation spectra were recorded by means of a Perkin Elmer LS50B Luminescence Spectrometer (Norwalk, CT) at the emission wavelength of 635 nm. A 15 nm slit width and a 1.0×0.4 cm^2 quartz cuvette were used for the measurements.

The emission spectra of the UV lamps were recorded by using fiber-coupled spectrometers (USB4000, Ocean Optics, Duiven, The Netherlands and Avantes AvaSpec-2048x14-USB2, The Netherlands, respectively).

2.4. HAL/UV-A and 8-MOP/UV-A treatments

The cells were collected from the cultivation flasks, centrifuged at 1400 rpm for 5 min and diluted in the serum-free RPMI 1640 medium to a density of 37.5×10^5 cells/ml. Eighty microliters of cell suspension was portioned into 96-well plates. After the addition of 10 μl of HAL solution or serum-free RPMI 1640 medium (controls), the cells were incubated for 4 h in the darkness at 37 °C. Approximately 5 min before the end of incubation with HAL, 10 μl of 8-MOP solution or serum-free RPMI 1640 medium (controls), was added to the wells. After 4-hour incubation with HAL and 5-min incubation with 8-MOP, the samples were irradiated with UV-A at the exposure times as indicated in the Results section. A home-made UV-A lamp (Sørensen UV-A lamp, Phillips Th 20W/09) emitting light mainly in the region of 340–410 nm was used (Fig. 1).

2.5. In vitro cell proliferation assay

Cell proliferation was assessed with a commercially available kit using a colorimetric method based on the cellular conversion of a tetrazolium compound (3-(4,5.dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt, MTS) into a formazan product, which can be detected by 492 nm absorbance. Twenty four hours after irradiation, 20 μl of MTS (Promega Corporation, Madison, WI) was added to each well. Absorbance at 492 nm was measured after 1 h of

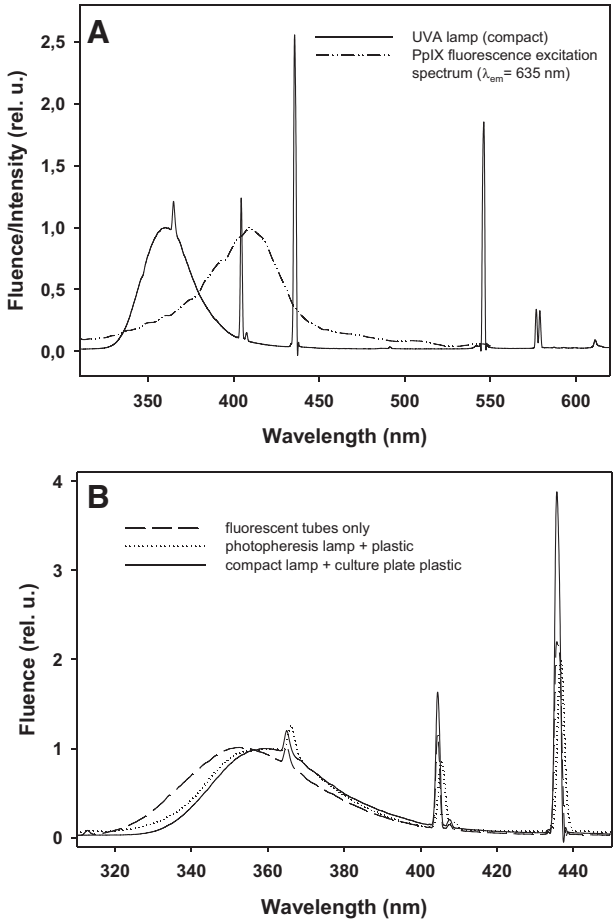

Fig. 1. (A) Normalized fluorescence excitation spectrum of HAL-induced PpIX in Jurkat cells and normalized emission spectrum of UV-A lamp. (B) Spectra of emitted light by UV-A lamps under different settings (compact lamp used in our laboratory covered with plastic culture plate, fluorescent tubes of the lamp used in our laboratory, lamp of the clinically used photopheresis system).

incubation at 37 °C by means of a well plate reader (Multiskan Ex, Labsystems, Finland).

2.6. In vitro long term cell survival assay

Methylcellulose-based medium human MethoCult® with recombinant cytokines (H4034, StemCell Technologies, France) was used for survival assay. Immediately after treatments, 120 μl of serum-free RPMI 1640 medium containing 200 Jurkat cells was added to 1.2 ml of MethoCult®. The samples were treated according to the manufacturer's instructions and suspensions were transferred into 35 mm Petri dishes. They were incubated at 37 °C in a humidified incubator with 5% CO_2.

2.7. Assessment of apoptotic cells

Apoptotic cells were identified by fluorescence microscopy based on nuclear morphology after staining with 4.0 μg/ml Hoechst 33342 (Sigma, St. Louis, MO) at 37 °C for 10 min. This assay was verified in our previous experiments [5]. The filter combination consisted of a 330 to 380 nm excitation filter, a 400 nm beam splitter, and a 420 nm long-pass emission filter. 2.5 μg/ml of propidium iodide (PI) was also added to the samples to confirm cell death. For PI fluorescence detection, the filter combination consisted of a 540/25 nm excitation filter, a 565 nm beam splitter, and a 605/55 nm band-pass emission filter. Fluorescence images were captured by a highly light sensitive thermo-electrically cooled charge-coupled device camera ORCAII-ER (Hamamatsu, Japan).

2.8. Statistical analysis

For statistical evaluation of data and curve fittings, the Sigma plot software was used. The Student's t-tests were applied for statistical analysis.

3. Results

3.1. Spectral measurements

The fluorescence excitation spectrum of cellular HAL-induced PpIX was measured in the suspension of Jurkat cells incubated with HAL in serum-free medium for 4 h. The spectra of lights emitted by the lamp used in our laboratory and by the light source of the clinically used Therakos photopheresis system were measured under various settings (compact lamp, fluorescent tubes only, light transmitted through plastic, etc.).

From the comparison of the measured spectra (Fig. 1A) two conclusions can be drawn. First, the emission spectra of both lamps partially overlap the excitation spectrum of cellular HAL-induced PpIX. Second, the light emitted by UV lamps depends on the settings (Fig. 1B).

3.2. Treatment with HAL and UV-A light

The fluorescence excitation spectrum of HAL-induced PpIX produced in cells has shown a considerable overlap with the emission spectrum of the UV-A lamps used in the present study (Fig. 1A). The sensitivity of Jurkat and Karpas 299 cells to HAL-mediated PDT was therefore examined after irradiation of the cells with UV-A light. Cell proliferation in both cell lines, evaluated by MTS assay, was found to decrease in a concentration-dependent manner, but the Karpas 299 cells were more resistant to this treatment (Fig. 2A & B). In addition, the effect of serum on the samples was tested in the Jurkat cells. The same results, within experimental error, were obtained when serum (FBS, final concentration of 10%) was added to the cells after UV-A irradiation (Fig. 2C).

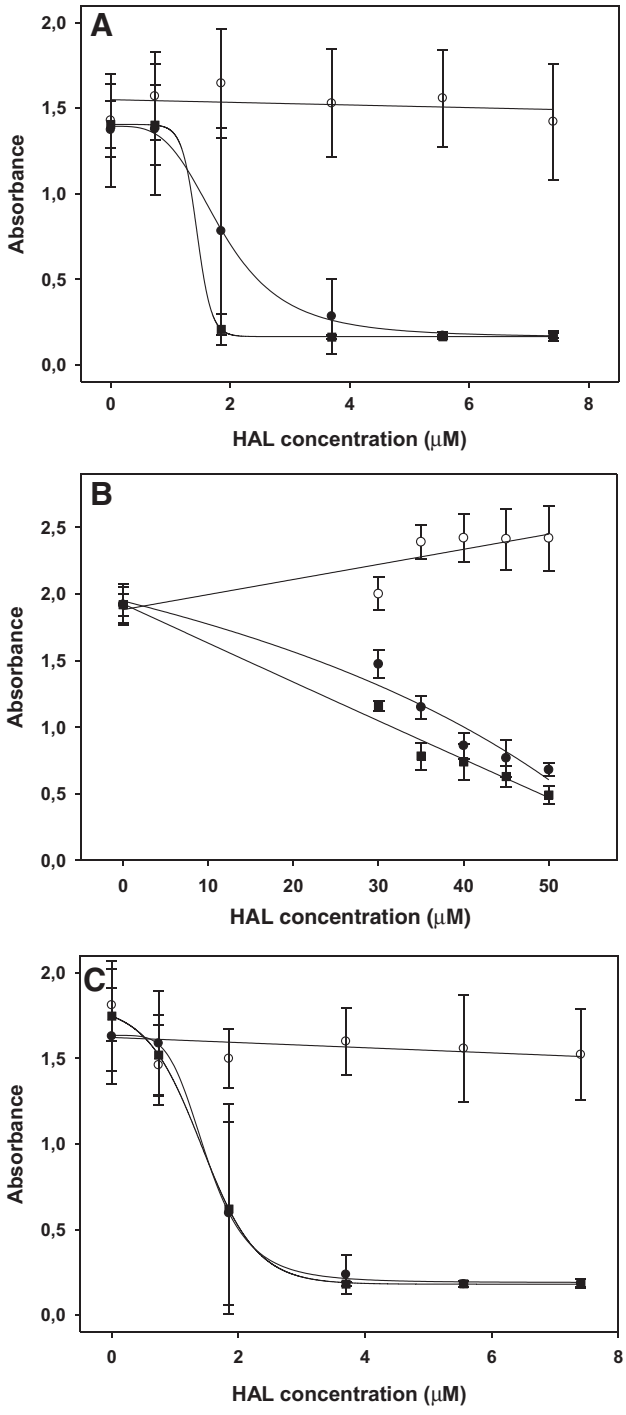

Fig. 2. Photodynamic inactivation of Jurkat and Karpas 299 cells using HAL and UV-A. (A) UV-A irradiation by the fluorescent tubes as shown in Fig. 1 in the Jurkat cells; (○) control (no irradiation), (●) 5 min, (■) 10 min irradiation. (B) The same as (A), but in the Karpas 299 cells. (C) The same as (A) in the Jurkat cells, but FBS added to the samples (final concentration of 10%) after UV-A irradiation. Each data point represents an average ± S.D. from at least 4 different cell samples.

These results clearly show that HAL can be used in combination with the Therakos UV-A light to photoinactivate human T-cell lymphoma cells.

3.3. Treatment with 8-MOP and UV-A light

The photosensitivity of Jurkat and Karpas 299 cells to the combined treatment with 8-MOP and UV-A light was first tested in the absence of

HAL. An increase in 8-MOP concentration in the samples resulted in decreasing cell proliferation as measured by MTS assay (Fig. 3A & B) in both cell lines. Such cell-killing effect was also enhanced with increasing UV-A irradiation time (Fig. 3A & B). In line with the action spectrum of 8-MOP (e.g. [15]), the effect of 8-MOP is expected to be dependent on the spectral range of the emission spectrum of the UV-A lamp. Indeed, the ability of 1.00 μM 8-MOP to sensitize the Jurkat cells to photoinactivation was significantly increased when the spectrum of the UV-A lamp was shifted by only few nanometers (Fig. 4). The results clearly document that the effect of 8-MOP is highly dependent on the spectral region of UV-A light in the human T-cell lymphoma cells.

3.4. Treatment with the combination of HAL, 8-MOP and UV-A light

Since both HAL and 8-MOP can generate an effect of cell photoinactivation after UV-A light irradiation, the possibility of using combination of the two drugs at reduced concentrations was tested. For this purpose four combinations of 8-MOP and HAL were explored in the Jurkat cells: 0.10 μM 8-MOP + 1.55 μM HAL or 0.10 μM 8-MOP + 5.00 μM HAL followed by 10 min UV-A light irradiation; and 0.50 μM 8-MOP + 1.55 μM HAL or 0.50 μM 8-MOP + 5.00 μM HAL followed by 5 min UV-A exposure. A significantly lower cell proliferation could be achieved after the incubation of the Jurkat cells with 0.10 μM 8-MOP + 1.55 μM HAL as compared to corresponding concentrations of 8-MOP or HAL alone if followed by 10 min UV-A irradiation. A similar effect could be achieved with the combination of 0.50 μM 8-MOP + 1.55 μM HAL if followed by 5 min UV-A irradiation. The effects of the treatments are presented as percentages of inhibition of cellular proliferation in Fig. 5. Qualitatively, the same results were obtained when serum (10% FBS) was added to the samples after UV-A irradiation (data not shown). A HAL concentration of 5.00 μM was sufficient to decrease the Jurkat cell proliferation to minimum after light exposure (Fig. 2A), therefore, the effect of combination with 8-MOP could not be tested. The data thus demonstrate the possibility of cell photoinactivation by the combination of 8-MOP with HAL, each given at concentrations lower than those alone necessary for the cell photoinactivation.

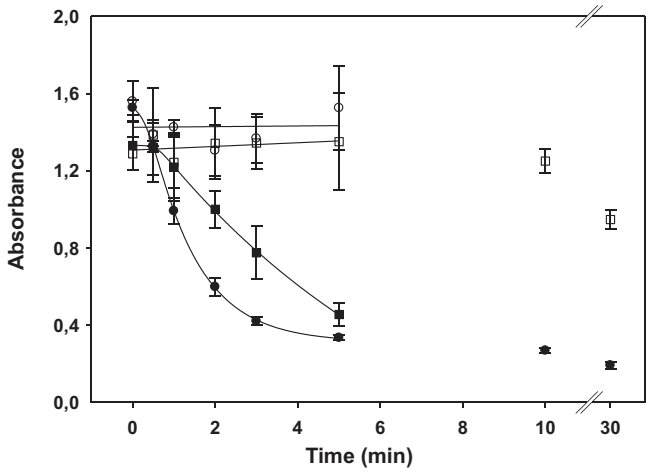

Fig. 4. Dependence of Jurkat cell photoinactivation by 8-MOP on UV-A light source. The cells were incubated with 1.00 μM 8-MOP and samples were irradiated by lights with spectra shown in Fig. 1, fluorescent tubes only (●) and whole lamp (■); (○, □) controls (no irradiation). Each data point represents an average ± S.D. from 6 different cell samples except from 10 min and 30 min time points, where only 4 and 2 samples, respectively were used.

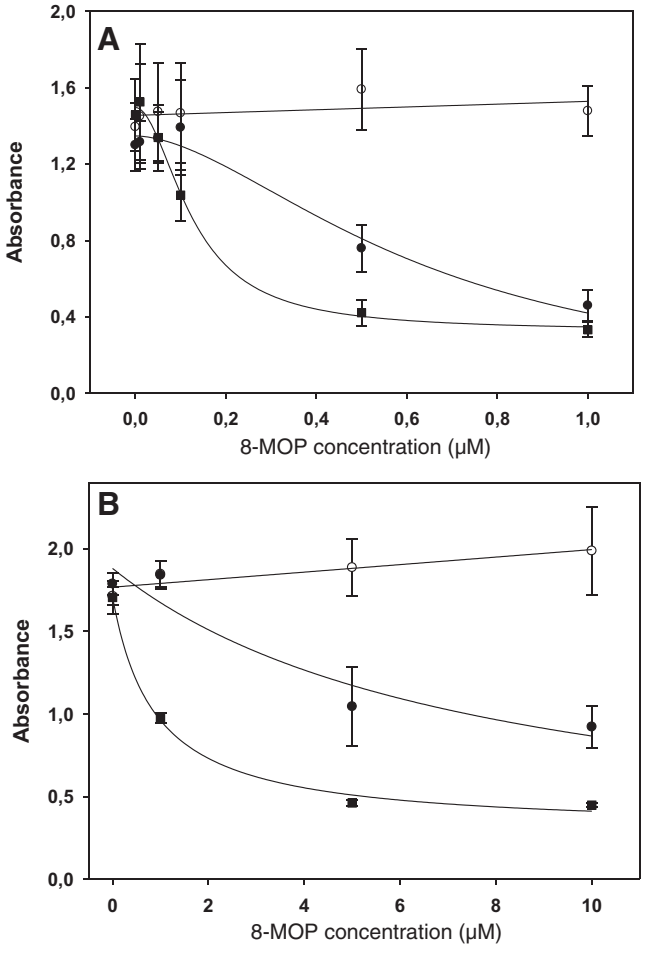

Fig. 3. Photoinactivation of Jurkat and Karpas 299 cells using 8-MOP and UV-A light irradiation. (○) Control (no irradiation), (●) 5 min, (■) 10 min irradiation in the Jurkat cells (A) and (●) 10 min, (■) 20 min irradiation in the Karpas 299 cells (B). The samples were irradiated by the compact lamp with the spectrum shown in Fig. 1. Each data point represents an average ± S.D. from 6 different cell samples.

3.5. Dark toxicity

8-MOP binds to DNA raising concerns about its toxicity. HAL may also be toxic when given systemically. Therefore, in each experiment, samples treated with the drugs but not with the light were included to check for the dark toxicity of the drugs. In general, there was no

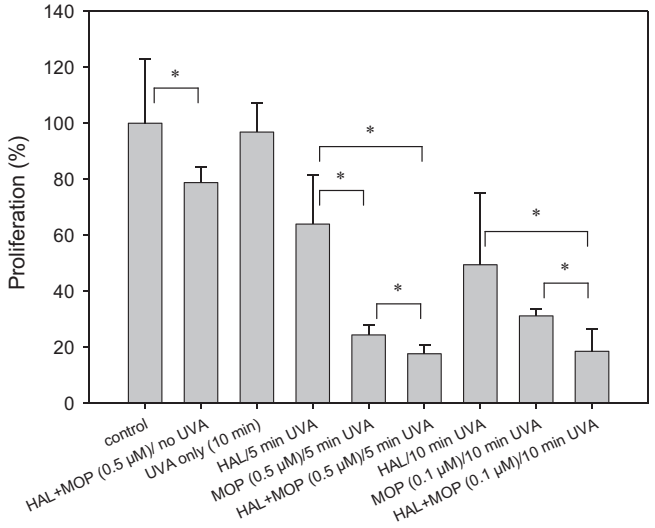

Fig. 5. Photoinactivation of Jurkat cells by using combination of HAL with 8-MOP and irradiation by UV-A light. The data for 1.55 μM HAL are shown. The samples were irradiated by the fluorescent tube light with the spectrum shown in Fig. 1. The data are expressed relative to control. The bars represent an average ± S.D. from 8 different cell samples.

indication for dark toxicities of HAL in the Jurkat and Karpas 299 cells up to 8 and 50 μM (Figs. 2 & 6) or of 8-MOP up to 1 and 10 μM (Figs. 3, 4, 6) based on the data of MTS assay. Slightly lower cell proliferation rates were found when combinations of the drugs were used to treat the Jurkat cells (Fig. 6).

3.6. Long term cell survival

All treatment regimes tested resulted in decreases in Jurkat cell proliferation. To check whether the decrease in cell proliferation correlated with long term cell death, a clonogenic assay in a semisolid medium was employed after the following treatments: 1.0 μM 8-MOP/10 min UV-A, 5.0 μM HAL/10 min UV-A, and 0.1 μM 8-MOP + 1.55 μM HAL/10 min UV-A. Surprisingly, a week after the cell seeding, in none of the treated samples compact colonies could be found, although the colonies were expected to form in such special medium [16–18]. In control samples, however, numerous living single cells were seen. After two weeks, spread and overlapping areas of high cell densities appeared in the control samples, which covered almost the whole area of the dishes. Consistent with the presence of living, metabolizing cells, a yellowish change of the medium color was noticed in the control samples (Fig. 7). Still no living cells were seen in the samples treated with 8-MOP- or/and HAL-UV-A.

3.7. Cell death assessment

All treatments tested in the present study (8-MOP/UV-A, HAL/UV-A, MOP + HAL/UV-A) could induce death of Jurkat and Karpas 299 cells in a drug or light dose-dependent manner. Twenty hours following the treatments, the cells were analyzed by fluorescence microscopy in order to check whether the modes of cell death differ depending on the treatment modality. There were considerable differences in the contents of apoptotic bodies present in the samples. Almost all the cells seemed to die by apoptosis after the treatment with 8-MOP followed by UV-A in both cell lines. However, the amount of apoptotic bodies among dead cells in the samples treated with HAL was dependent on the treatment regimen (Fig. 8) (Table 1). Quantitative evaluation was not possible due to the disintegration of apoptotic cells.

4. Discussion

In the present study we have tested HAL in combination with UV-A to inactivate T-cell lymphoma Jurkat and Karpas 299 cell lines as in vitro models of cutaneous T-cell lymphoma and compared the effects with those achieved after typical treatment of the cells with 8-MOP and UV-A irradiation.

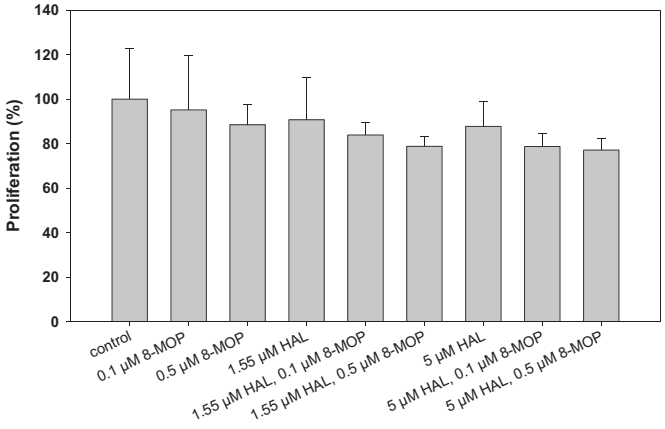

Fig. 6. Dark toxicity (relative to control). The Jurkat cells were treated with indicated drugs and doses, but the samples were not irradiated by light. The bars represent an average ± S.D. from at least 6 different cell samples.

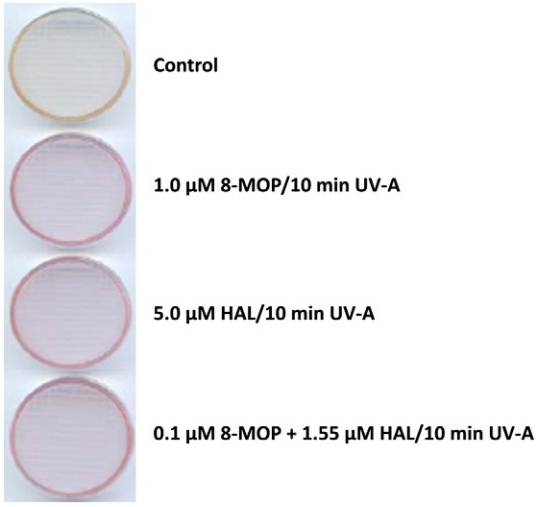

Fig. 7. Cell survival assay. Change in the color of the medium only in the control sample three weeks after seeding the cells — consistent with the presence of living, metabolizing cells.

Decrease in both proliferation and survival of Jurkat and Karpas 299 cells could be induced by the treatment with HAL and UV-A irradiation. This is not surprising due to a partial overlap between excitation spectrum of PpIX and the emission spectrum of UV-A lamp used in this study. Such results are in agreement with results of another study in which the combination of ALA and UV-A was tested in the T-cell lymphoma HUT-78 cell line for the purposes of PUVA treatment [19].

Depending on the treatment regimen used, differences could be seen in the mode of cell death. While only apoptosis was induced when cells were treated with 8-MOP and UV-A light, the parameters such as HAL concentration and UV-A irradiation time affected the mode of the death of the Jurkat and Karpas 299 cells in the case of HAL-induced cell photoinactivation.

As discussed in several publications, the therapeutic effect of ECP in vivo is not caused by cell inactivation only, but additionally relies on the induction of immune response (for references see [20]). In this regard, it is important to mention that several publications discussed the significance of the mode of cell death for induction of immune effects [21–25]. It has been recognized that viable cells are able to discriminate apoptotic from necrotic targets via distinct cell surface receptors and such receptors can induce signaling events that differ for apoptotic as compared to necrotic targets [26]. Our data show that apoptosis is induced by 8-MOP-UV-A and the clinical experience indicates that this mode of cell death is efficient to achieve a treatment effect of photophoresis. Apoptosis as well as necrosis could be induced by HAL-UV-A in the present study and the question is whether appearance of necrotic cells would be beneficial for the treatment outcome. In this respect, immunopotentiation induced by PDT has been documented in numerous publications (reviewed in e.g. [12,27]). Importantly, vaccines and lysates generated by exogenous photosensitizer-mediated PDT were shown to be more effective than those generated by means of UV and ionizing irradiations or a freeze–thaw technique [28–30]. Improved effect of PDT-generated vaccines has been ascribed to the concurrent appearance of necrotic and apoptotic cells under PDT treatment protocols contrary to the presence of pure apoptotic or pure necrotic cells under UV or ionizing radiation protocols, respectively [28]. It should be mentioned, however, that under certain conditions, PDT was reported to cause immunosuppression as well (for references see [27]).

ECP is a recommended treatment of CTCL and there is fair evidence to support its use in GvHD [1]. However, many patients experience refractory disease, thus further development of the current ECP regime may hopefully be of benefit to patients.

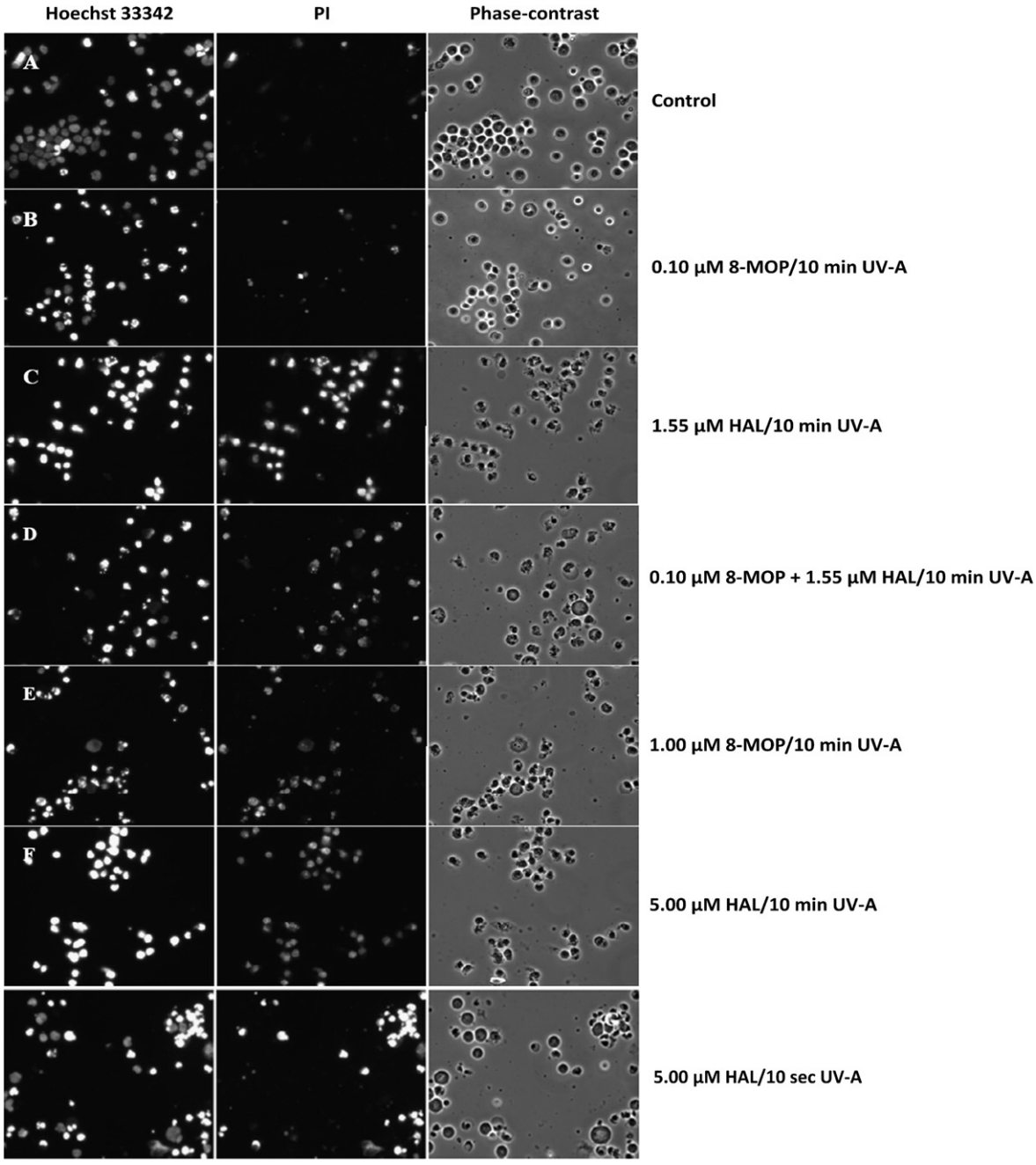

Fig. 8. Fluorescence images of Jurkat cells after different treatments (as indicated) showing nuclear morphology after staining with Hoechst 33342 (left column) and PI (middle column). Phase contrast images are shown in the right column. The UV-A light was the fluorescent tubes with the spectrum shown in Fig. 1B.

Based on the data of the present study, we can conclude that HAL is effective for the photoinactivation of T-cell lymphoma Jurkat and Karpas 299 cell lines after using a UV-A lamp with an emission spectrum similar to that of the light source used in the commercial Therakos photopheresis system. HAL-UV-A can induce both apoptosis and necrosis of the Jurkat and Karpas 299 cells and may thus provide a potential option for enhanced efficacy of ECP. If HAL should be used for ECP, the treatment conditions need to be optimized in subjects with an intact immune system to achieve induction of a desirable immune response.

Table 1
Assessment of the mode of cell death after HAL/UV-A-induced photoinactivation (quantitative evaluation was not possible due to the disintegration of apoptotic cells).

Drug concentration	UV-A irradiation	Cell appearance 20 h after treatment
1.55 μM HAL	10 min	Most apoptotic + some alive or most necrotic + some apoptotic[a]
5.00 μM HAL	10 min	Only necrotic, no apoptotic
5.00 μM HAL	10 s	Apoptotic + alive (similar proportions)
1.55 μM HAL + 0.10 μM 8-MOP	10 min	Almost only apoptotic + few alive

[a] Sample to sample variations.

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References

[1] J.J. Scarisbrick, P. Taylor, U. Holtick, et al., Photopheresis Expert Group. U.K. consensus statement on the use of extracorporeal photopheresis for treatment of cutaneous T-cell lymphoma and chronic graft-versus-host disease, Br. J. Dermatol. 158 (2008) 659–678.
[2] A.K. Gupta, T.F. Anderson, Psoralen photochemotherapy, J. Am. Acad. Dermatol. 17 (1987) 703–734.
[3] Q. Peng, K. Berg, J. Moan, et al., Review: 5-Aminolevulinic acid-based photodynamic therapy: principle and experimental research, Photochem. Photobiol. 65 (1997) 235–251.
[4] Q. Peng, T. Warloe, K. Berg, et al., Review: 5-Aminolevulinic acid-based photodynamic therapy: clinical research and future challenges, Cancer 79 (1997) 2282–2308.
[5] I.E. Furre, M.T. Møller, S. Shahzidi, et al., Involvement of both caspase-dependent and -independent pathways in apoptotic induction by hexaminolevulinate-mediated photodynamic therapy in human lymphoma cells, Apoptosis 11 (2006) 2031–2042.
[6] I.E. Furre, S. Shahzidi, Z. Luksiene, et al., Targeting PBR by hexaminolevulinate-mediated photodynamic therapy induces apoptosis through translocation of apoptosis-inducing factor in human leukemia cells, Cancer Res. 65 (2005) 11051–11060.
[7] J.M. Gaullier, K. Berg, Q. Peng, et al., The use of esters of 5-aminolevulinic acid to improve photodynamic therapy on cells in culture, Cancer Res. 57 (1997) 1481–1486.
[8] Q. Peng, J. Moan, T. Warloe, et al., Build-up of esterified aminolevulinic-acid-derivative-induced porphyrin fluorescence in normal mouse skin, J. Photochem. Photobiol. B 34 (1996) 95–96.
[9] M. Burger, H.B. Grossman, M. Droller, et al., Photodynamic diagnosis of non-muscle-invasive bladder cancer with hexaminolevulinate cystoscopy: a meta-analysis of detection and recurrence based on raw data, Eur. Urol. 64 (2013) 846–854.
[10] K. Rittenhouse-Diakun, H. Van Leengoed, J. Morgan, et al., The role of transferrin receptor (CD71) in photodynamic therapy of activated and malignant lymphocytes using the heme precursor delta-aminolevulinic acid (ALA), Photochem. Photobiol. 61 (1995) 523–528.
[11] E.A. Hryhorenko, K. Rittenhouse-Diakun, N.S. Harvey, et al., Characterization of endogenous protoporphyrin IX induced by delta-aminolevulinic acid in resting and activated peripheral blood lymphocytes by four-color flow cytometry, Photochem. Photobiol. 67 (1998) 565–572.
[12] A. Casas, C. Perotti, H. Fukuda, A.M. del C Battle, Photodynamic therapy of activated and resting lymphocytes and its antioxidant adaptive response, Lasers Med. Sci. 17 (2002) 42–50.
[13] A. Castano, P. Mroz, M.R. Hamblin, Photodynamic therapy and anti-tumor immunity, Nat. Rev. Cancer 6 (2006) 535–545.
[14] S.O. Gollnick, C.M. Brackett, Enhancement of anti-tumor immunity by photodynamic therapy, Immunol. Res. 46 (2010) 216–226.
[15] B. Ortel, R.W. Gange, An action spectrum for the elicitation of erythema in skin persistently sensitized by photobound 8-methoxypsoralen, J. Invest. Dermatol. 94 (1990) 781–785.
[16] A. Galietta, R.H. Gunby, S. Redaelli, et al., NPM/ALK binds and phosphorylates the RNA/DNA-binding protein PSF in anaplastic large-cell lymphoma, Blood 110 (2007) 2600–2609.
[17] M. Fakler, S. Loeder, M. Vogler, et al., Small molecule XIAP inhibitors cooperate with TRAIL to induce apoptosis in childhood acute leukemia cells and overcome Bcl-2-mediated resistance, Blood 113 (2009) 1710–1722.
[18] A. Nahimana, A. Attinger, D. Aubry, et al., The NAD biosynthesis inhibitor APO866 has potent antitumor activity against hematologic malignancies, Blood 113 (2009) 3276–3286.
[19] Y. Akita, D. Watanabe, T. Yanagishita, et al., The effect of psoralen plus ultraviolet A in vitro in HUT-78 enhances by 5-aminolevulinic acid, Photodermatol. Photoimmunol. Photomed. 23 (2007) 95–97.
[20] R. Broady, J. Yu, M.K. Levings, Pro-tolerogenic effects of photodynamic therapy with TH9402 on dendritic cells, J. Clin. Apher. 23 (2008) 82–91.
[21] A. Melcher, M. Gough, S. Todryk, R. Vile, Apoptosis or necrosis for tumor immunotherapy: what's in a name? J. Mol. Med. 77 (1999) 824–833.
[22] R.E. Cocco, D.S. Ucker, Distinct modes of macrophage recognition for apoptotic and necrotic cells are not specified exclusively by phosphatidylserine exposure, Mol. Biol. Cell 12 (2001) 919–930.
[23] S.R. Scheffer, H. Nave, F. Korangy, et al., Apoptotic, but not necrotic, tumor cell vaccines induce a potent immune response in vivo, Int. J. Cancer 103 (2003) 105–111.
[24] S. Basu, R.J. Binder, R. Suto, et al., Necrotic but not apoptotic cell death releases heat shock proteins, which deliver a partial maturation signal to dendritic cells and activate the NF-kB pathway, Int. Immunol. 12 (2000) 1539–1546.
[25] P.K. Srivastava, Hypothesis: controlled necrosis as a tool for immunotherapy of human cancer, Cancer Immun. 3 (2003) 4.
[26] V.A. Patel, D.J. Lee, A. Longacre-Antoni, et al., Apoptotic and necrotic cells as sentinels of local tissue stress and inflammation: Response pathways initiated in nearby viable cells, Autoimmunity 42 (2009) 317–321.
[27] W.R. Chen, Z. Huang, M. Korbelik, et al., Photoimmunotherapy for cancer treatment, J. Environ. Pathol. Toxicol. Oncol. 25 (2006) 281–291.
[28] S. Gollnick, L. Vaughan, B.W. Henderson, Generation of effective antitumor vaccines using photodynamic therapy, Cancer Res. 62 (2002) 1604–1608.
[29] S.-M. Bae, Y.-W. Kim, S.-Y. Kwak, et al., Photodynamic therapy-generated tumor cell lysates with CpG-oligodeoxynucleotide enhance immunotherapy efficacy in human papillomavirus 16 (E6/E7) immortalized tumor cells, Cancer Sci. 98 (2007) 747–752.
[30] M. Korbelik, J. Sun, Photodynamic therapy-generated vaccine for cancer therapy, Cancer Immunol. Immunother. 55 (2006) 900–909.