Photofrin Photodynamic Therapy Can Significantly Deplete or Preserve Oxygenation in Human Basal Cell Carcinomas during Treatment, Depending on Fluence Rate

Barbara W. Henderson, Theresa M. Busch, Lurine A. Vaughan, Noreen P. Frawley, Debra Babich, Tara A. Sosa, Joseph D. Zollo, Anthony S. Dee, Michele T. Cooper, David A. Bellnier, William R. Greco, and Allan R. Oseroff


Abstract

At high fluence rates in animal models, photodynamic therapy (PDT) can photochemically deplete ambient tumor oxygen through the generation of singlet oxygen, causing acute hypoxia and limiting treatment effectiveness. We report that standard clinical treatment conditions (1 mg/kg Photofrin, light at 630 nm and 150 mW/cm²), which are highly effective for treating human basal cell carcinomas, significantly diminished tumor oxygen levels during initial light delivery in a majority of carcinomas. Oxygen depletion could be found during at least 40% of the total light dose, but tumors appeared well oxygenated toward the end of treatment. In contrast, initial light delivery at a lower fluence rate of 30 mW/cm² increased tumor oxygenation in a majority of carcinomas. Laser treatment caused an intensity- and treatment-time-dependent increase in tumor temperature. The data suggest that high fluence rate treatment, although effective, may be inefficient.

Introduction

PDT is a recently approved treatment of esophageal and lung tumors, which is also in trials for multiple other cancers. PDT is believed to act principally through the production of cytotoxic singlet oxygen (¹O₂), formed when the photosensitizer absorbs light and transfers its energy from its excited triplet state to ground-state molecular oxygen (O₂ Ref. 1). The rate of ¹O₂ production depends on the light fluence rate, photosensitizer absorption coefficient and concentration, and the tissue availability of O₂ (2). Using the FDA-approved photosensitizer Photofrin, diffusion models (3) and preclinical studies by us and others (4–6) show that at high fluence rates, rapid photochemical conversion of O₂ to ¹O₂ can deplete intracellular state oxygen, limiting the photodynamic process and tumor control (5, 6). In addition, oxygen availability also can be limited by effects of PDT on microvasculature (7).

The occurrence of oxygen depletion in clinical Photofrin-PDT has been unknown. Because of the complexity of clinical trials, there is little information whether effective treatment conditions also are optimal. Using empirically derived parameters of 1 mg/kg Photofrin with 150 mW/cm² irradiance and a light dose ~215 J/cm², we have found PDT highly effective for human BCCs, with a >90% durable complete response rate. We report highly significant and opposing changes in tumor oxygenation levels during treatment of nBCCs with Photofrin-PDT, using both “standard” and reduced light fluence rates. The data suggest that the efficiency of clinical PDT might be improved by reduced fluence rates.

Materials and Methods

Patients and PDT Treatment. Between December 1995 and October 1999, 22 carcinomas in eight patients who presented with nBCCs and underwent PDT with the photosensitizer Photofrin were evaluated. Of these patients, one had one lesion only. The others, suffering from the genetic disorder nevoid BCC syndrome, had numerous lesions. In two patients, different BCCs were examined during several repeat visits to the clinic. However, none of the lesions included in this study had received any previous treatment. To be included in the study, tumors had to be at least 2 mm in thickness above the skin surface and devoid of overt hemorrhage or necrosis. Lesion dimensions were determined by digital caliper measurement, and tumor volume was estimated using the formula (4/3)πabc, where a, b, and c are the radii of length, width, and height of the lesion. For PDT treatment, patients received 1 mg/kg Photofrin, followed by illumination with 630 nm light after an interval of 48–72 h. The total treatment fluence was 215 J/cm². The study was approved by the Institutional Review Board, and all patients signed informed consent.

Measurement of Tumor pO₂. Inratumor pO₂ was measured in resting, awake patients using a polarographic device (Eppendorf pO₂ Histograph; Eppendorf Scientific, Inc., Madison, WI; Refs. 8 and 9). Before and between measurements, the instrument was calibrated in 0.9% sterile saline bubbled alternately with air and nitrogen to set 100 and 0% pO₂ currents. Ambient air pressure and tumor temperature (measured using an Omega HY-0 30 gauge, ½-inch needle thermocouple) were recorded and used to postcalibrate the data. Before measurement commenced, each lesion was cleansed with betadine and anesthetized with 2% lidocaine without vasoconstricting agent. The 300-μm-diameter polarographic needle probe was aligned at the tumor surface, and the probe was advanced one step to ensure the tip was within the tumor, and automatic probe advancement was begun after the pO₂ values had stabilized. Probe advancement was set to a 0.7-mm forward step and a 0.3-mm retraction step for each reading. Probe track lengths and number of tracks measured were determined according to tumor dimensions. Tracking through the tumor was parallel to the skin surface at a depth of ~1–3 mm, and care was taken to choose comparable track positions (depth and tumor periphery versus center) for control and experimental measurements, as well as to keep tracks physically well separated from each other. One to three tracks per tumor were measured for each experimental condition (see below), with a maximum of six tracks per tumor. Averages of 28 ± 3 (SE) and 38 ± 5 measured values per lesion were accumulated for pre-PDT and during-PDT conditions, respectively. Tumor temperature was recorded by inserting the thermocouple into each track immediately after oxygen measurements. During the entire procedure, the patient’s arterial oxyhemoglobin saturation was monitored by a pulse oximeter (median for all patients, 97.0%; range, 94.0%–98.0%).

The effects of PDT on tumor oxygenation were evaluated at two fluence rates. Considering the known large variability of oxygen levels among different tumors (10), the experiments were designed so that each tumor provided its own control.

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2 To whom requests for reprints should be addressed, at Photodynamic Therapy Center, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263. Phone: (716) 845-4429. Fax: (716) 845-8920.
3 Present address: Department of Radiation Oncology, School of Medicine, University of Pennsylvania, Philadelphia, PA 19104.
4 The abbreviations used are: PDT, photodynamic therapy; BCC, basal cell carcinoma; nBCC, nodular basal cell carcinoma; PDT MODEM, PDT molecular oxygen-depletion model.

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For the 150 mW/cm² fluence rate group, baseline pO₂ values of the lesion under study were measured immediately before light treatment, and the lesion was illuminated at 150 mW/cm². In 8 carcinomas, pO₂ was again measured during light exposure at selected time points between 0.5 and 10 min (4.5–90 J/cm²) without interruption of laser light; care was taken to record the illumination time elapsed (i.e., fluence delivered) during these measurements. In five lesions, pO₂ was measured near completion of treatment, between 15 and 20 min (135–180 J/cm²) of light exposure. After completion of measurements, the remainder of the total 215 J/cm² treatment fluence was delivered at 150 mW/cm² without interruption, according to current standard practice for patient benefit.

Two mechanisms could be invoked as the cause for the observed changes: photochemical consumption of oxygen and changes in vascular supply. In rodent models, photochemical oxygen depletion as well as vessel constriction can occur very rapidly during PDT, which was observed in this study. Tissue samples from biopsies of lesions other than those designated for pO₂ studies and from surgically removed tumor tissue were examined for photofrin content. Freshly obtained tissue was dissolved in Solvable, followed by porphyrin-specific fluorescence detection as described earlier (11).

Results and Discussion

This study is the first to probe the effects of clinical PDT on tumor oxygenation. We initially examined “standard” treatment irradiance of 150 mW/cm² with 1 mg/kg Photofrin. Over the past years, we have used this fluence rate with a ~200 J/cm² fluence in >1500 superficial and nodular BCCs, with an initial complete response rate >90%, determined at 6 months after treatment; the response was quite durable past 5 years (13). Thus, we did not expect the above treatment conditions to cause substantial depletion in oxygen during the course of treatment.

150 mW/cm² Fluence Rate PDT Can Deplete Tumor Oxygen. Intratumor pO₂ was assessed before and during treatment in the first eight nBCC lesions accrued that met the criteria for pO₂ measurements. Baseline, pre-PDT values for pO₂ were shown together with tumor temperature for each lesion in Fig. 1A and summarized in Table 1. Median pO₂ levels ranged from ~2–50 mm Hg. There was a linear increase in tumor temperature with pO₂ up to ~34°C and 20 mm Hg; above 20 mm Hg, the temperature was relatively constant. Because tumor temperatures depend on vascular perfusion, the relationship is not unexpected. Initial tumor temperatures appeared to depend, at least in part, on ambient room temperatures, which varied by about 2°C. Lesion temperatures during PDT were dominated by heating attributable to laser irradiation (see below).

Statistical Considerations.

To determine significant differences between median pO₂ values, as well as the proportions of values ≥2.5 mm Hg, before and during PDT, the pooled raw pO₂ values from all lesions for each fluence rate were analyzed by the Mann-Whitney test. The Wilcoxon signed rank test was used to examine for each lesion the statistical significance of differences in median pO₂ before and during PDT and proportion of values ≥2.5 mm Hg. The Student’s t test was used for comparison of all other measurements. P < 0.05 was considered to be significant.

The intratumor pO₂ data during PDT with 150 mW/cm² fluence rates are summarized in Table 1 and plotted for each lesion as a function of tumor temperature in Fig. 1B. When measured during lesion illumination between 0.5 and 10 min (4.5–90 J/cm²) light, six of the eight carcinomas had a decrease in median pO₂, with five lesions ≥10 mm Hg. BCC #5 had a drop of ~36 mm Hg. Despite pO₂ increases in two lesions, overall there was a significant decrease from baseline in the median of pO₂ values (from 25.4 to 9.2 mm Hg). Even more significant was the increase in values ≥2.5 mm Hg, which indicates severe hypoxia. The median frequency at which these low values were encountered increased almost 5-fold from 6.7% before PDT to 35.1% during PDT. In murine tumor models, marked shifts toward tumor hypoxia during PDT treatment have been demonstrated at high fluence rates, but these have been associated with treatment failures (5). Clinical follow up ≥6 months is available for six of the lesions (nos. 1, 2, 3, 4, 5, and 7), and all have had complete clinical responses.

Two mechanisms could be invoked as the cause for the observed changes: photochemical consumption of oxygen and changes in vascular supply. In rodent models, photochemical oxygen depletion as well as vessel constriction can occur very rapidly during PDT, whereas other vascular effects, such as thrombosis and vessel col-

1 A. R. Oseroff, manuscript in preparation.
OXYGENATION CHANGES IN HUMAN BASAL CELL CARCINOMAS DURING PDT

Table 1 Summary of oxygenation and thermal and size parameters from BCC lesions evaluated at two different fluence rates

<table>
<thead>
<tr>
<th>Fluence Rate</th>
<th>Median pO2 (mm Hg)</th>
<th>Median lesion thickness (mm)</th>
<th>Median tumor volume (cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 mW/cm²</td>
<td>179/227 (55.6–297.8)</td>
<td>6.3 (4.2–10.2)</td>
<td>2.16 (0.53–6.56)</td>
</tr>
<tr>
<td>300 mW/cm²</td>
<td>275/382 (80.7–493.7)</td>
<td>9.0 (5.7–15.1)</td>
<td>1.52 (0.29–8.13)</td>
</tr>
</tbody>
</table>

- N°: Number of lesions.
- N°: Number of measured pO2 values.
- % Decrease: Percentage of values ≤2.5 mm Hg from all pooled data (range of lesion % values, ≤2.5 mm Hg).
- P: Probability value (Mann-Whitney).
- 5%: Probability value (Wilcoxon rank test).

This analysis shows that oxygen depletion during PDT light exposure can be rapid and can persist through at least the initial 40% of the treatment. The data are consistent with a photochemical depletion process but do not exclude consequences of possible vascular constriction.

Although the combined data from all lesions measured during 150 mW/cm² illumination with ≤ 90 J/cm² light fluence indicate significant overall decreases in ground-state oxygen, the degree of depletion varied between carcinomas. An increase in median pO2 was found in two of the eight lesions (Fig. 1B). Photochemical oxygen depletion will depend on photosensitizer tissue content. Although we can measure in situ fluorescence from the Photofrin, we lack a proven noninvasive method to quantitate photosensitizer concentration. Therefore, to obtain an estimate of Photofrin tissue levels, we determined average porphyrin content in biopsies from seven BCCs not used for pO2 measurement from three of the study patients. These samples showed a 5-fold range of porphyrin levels (median, 0.53 µg/g; range, 0.29–1.59 µg/g). In mice, using typical treatment conditions of 5 mg/kg Photofrin, porphyrin levels were ~11 µg/g (6).

The lower levels of photosensitizer in human BCCs and the successful clinical outcomes raise the question as to whether photochemical oxygen depletion could be expected to occur. To answer this question, we calculated tissue oxygen levels as described by Foster et al. (3) using the PDT MODeM program (12) to simulate oxygen depletion for tissue Photofrin concentrations in the upper and lower range of the above-measured values. As seen in Fig. 2, this simulation predicts that oxygen will be depleted to severely hypoxic values (≤2.5 mm Hg) within the distance of 150 µm from the capillary by exposure to light at 150 mW/cm², if the lesion contained porphyrin concentrations above the median value of ~0.5 µg/g. Porphyrin concentrations below the median value (e.g., 0.2 µg/g) will cause moderate to minimal oxygen depletion. Although these calculations do not take into consideration effects such as photobleaching of the sensitizer and changes in blood supply, they nevertheless strongly suggest that the failure of some lesions to be oxygen depleted by high fluence rate was caused by their low photosensitizer content.

Other factors that might influence oxygen depletion are tumor thickness and volume, since they can affect both light penetration and blood supply. Analysis of these parameters, however, yielded no correlation with PDT-induced changes in tumor oxygenation (data not shown). There also was no correlation with measurements of Photofrin fluorescence at the surface of BCC or with tumor optical properties (data not shown).

In addition to the above lesions, the oxygenation changes in five nBCCs were examined at 15–20 min (135–180 J/cm²) of illumination, a point where ~60% of the treatment light dose had been delivered. Of these lesions, the median pO2 value remained unchanged in one and increased in the remaining four. Overall, the pooled data reveal an increase in median pO2 from 15.6 to 28.3 mm Hg. The proportion of values ≤2.5 mm Hg decreased from a baseline of 12.7 to 0.7%. Median tumor temperatures rose by 5.4°C (range, 3.1–7.9°C). The lack of oxygen depletion in these two lesions could be attributable to low porphyrin levels, as was suggested for lesions 7 and 8 in Fig. 1B. More likely, it was attributable to gradual photobleaching of the porphyrin during illumination. We found that Photofrin fluorescence measured at the tumor surface disappeared by the end of the irradiation, consistent with photobleaching (data not shown). Photosensitizer photobleaching was demonstrated by Georgakoudi et al. (15) in a spheroid model that showed a progressive decrease in photochemical oxygen consumption with sustained illumination that was consistent with theoretical calculations of sensitizer photobleaching. Our own studies in a rodent tumor model also support such a mechanism (6).

Finally, the data indicate that at least in these lesions, no vascular occlusion had occurred by the time 80% of the total treatment dose had been delivered.

**Fig. 2.** Simulated ground-state oxygen distribution, plotted by PDT MODeM as a function of the radial distance from a capillary, under different tissue porphyrin concentrations (µg/g) and fluence rate conditions (mW/cm²): 150 mW/cm²: ▲ 0.2 µg/g; ● 0.5 µg/g; ▪ 1.5 µg/g. 30 mW/cm²: ◻ 0.2 µg/g; □ 1.5 µg/g.

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30 mW/cm² Fluence Rate PDT Preserves or Increases Tumor Oxygenation. Both theoretical modeling (3) and preclinical studies have shown (6) that lowering the light fluence rate will reduce the rate of $^{1}O_2$ generation and therefore $O_2$ consumption. Calculation of $pO_2$ levels (Fig. 2) to be expected under illumination at a fluence rate of 30 mW/cm² and tumor porphyrin concentrations within the range determined in this patient population revealed that moderate oxygen depletion might occur at the highest measured porphyrin levels (1.5 µg/g). We therefore assessed $pO_2$ changes in the next group of nine BCC lesions before and during illumination at a fluence rate of 30 mW/cm² (Table 1; Fig. 1C). These lesions included the largest lesion evaluated (lesion 2), but the differences in overall lesion thickness or volume from the high fluence rate group were not statistically significant. Median baseline $pO_2$ values were slightly lower than in the high fluence rate group, but this difference was also not significant.

Upon illumination at 30 mW/cm² and measured at time points between 3 and 10 min of light (5.4–19 J/cm²), the fraction of volumes ≤2.5 mm Hg remained essentially unchanged. However, in six of the nine lesions, increases in median $pO_2$ were observed (median pre-PDT, 12.8 mm Hg; during PDT, 35.0 mm Hg), in contrast to the decrease in median $pO_2$ in the higher fluence rate group. The median change in $pO_2$ in these lesions was an increase of 11.7 mm Hg, with a maximum increase of ~45 mm Hg. Although there were small decreases in $pO_2$ in lesions 7, 8, and 9 (Fig. 1C), the overall increase among the nine lesions was highly significant when the data from all lesions were pooled (Table 1). These data are consistent with preclinical observations that lowering treatment fluence rate maintains or improves tumor oxygenation during PDT (3, 6).

To determine the role of the light dose delivered at the two fluence rates, we can compare tumor oxygenation after comparable fluences of 5–18 J/cm² [0.5–2 min at 150 mW/cm² (3 lesions); 3–10 min at 30 mW/cm² (9 lesions)]. Median $pO_2$ values decreased from 29.2 to 3.9 mm Hg, and the percentage of values ≤2.5 mm Hg increased from 14.3 to 45.3% in the higher fluence rate group, whereas in the lower fluence rate group, median $pO_2$ values increased and the percentage of values ≤2.5 mm Hg remained unchanged (see above). It is clear from this comparison that tumor oxygenation changes are dependent on fluence rate rather than fluence.

Table 2, which contains the data from 13 BCCs in two patients evaluated at both fluence rates, shows that the pattern of fluence rate-dependent changes in tumor oxygenation holds despite large intra- and interpatient variations. In both patients, the pooled lesion median $pO_2$ value decreased under illumination at 150 mW/cm², although oxygen in one lesion in patient A (lesion 7, Fig. 1B) increased. Oxygenation increased in five and declined slightly in two BCCs exposed to 30 mW/cm² light in both patients.

In patient B, lesions 1 and 2 (Fig. 1C) irradiated at 30 mW/cm² were characterized by very low baseline $pO_2$ values. Low baseline lesion temperatures in these cutaneous tumors were likely attributable to low ambient room temperature during that treatment session. All light exposures increased the tumor temperature as measured immediately after $pO_2$ measurement (Table 1). Both fluence rate groups showed a highly significant median lesion temperature increase of ~2°C, although the temperature in the two lesions with highest initial values (nos. 5 and 6, Fig. 1C) in the low fluence rate group declined slightly upon illumination. During treatment, the lesion temperature will be affected by both light energy deposited in the skin and by the blood flow, and our current data cannot distinguish these contributions. As evident from Fig. 1A, perfusion alone can account for tumor temperatures up to 34–35°C.

In summary, we have found that a clinically successful PDT treatment protocol using 150 mW/cm² irradiation with 1 mg/kg Photofrin can substantially deplete intratumor oxygenation in the majority of nodular BCCs. The oxygen depletion can extend at least through the first 40% of illumination, although it appears to have resolved after delivery of 80% of the light dose. Oxygen depletion and loss of efficacy might be expected to be even more significant at the 2 mg/kg Photofrin dose used in noncutaneous carcinomas (1). A lower fluence rate of 30 mW/cm² can minimize or abrogate oxygen depletion. Lesions sampled for Photofrin content showed a 5-fold variation in photosensitizer levels, and a wide range of oxygen depletions also was found. Thus, it is likely that the differences in oxygenation were attributable, at least in part, to biological variations in photosensitizer content, as well as to differences in vascularity.

There are several possibilities as to why Photofrin-PDT at 150 mW/cm² is clinically successful, despite the apparent oxygen depletion. Oxygen-independent, type I processes might play a role in human phototoxicity, although this has not been observed in preclinical models (16), BCCs are relatively indolent tumors that might respond to PDT-induced inflammation or disturbance of tissue stroma [e.g., in the 29% placebo response in studies of intralosomal interferon therapy (17)]. PDT also can affect host immune responses (1, 18, 19), which might contribute to tumor responses. Endothelial cells in the carcinoma and surrounding stroma will have the highest oxygen levels, and delayed vascular damage and collapse might lead to eventual tumor control. More importantly, it is likely that Photofrin photobleaching during illumination eventually lowers the sensitizer level to the point where oxygen consumption is reduced, an assump-

### Table 2 Changes in tumor oxygenation in two patients during PDT at high and low fluence rates

<table>
<thead>
<tr>
<th>Patient A</th>
<th>150 mW/cm²</th>
<th>30 mW/cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median $pO_2$ pre-PDT in mm Hg</td>
<td>23.2 ± 7.3 (14.3, 30.4, 37.2)</td>
<td>28.7 (10.4, 55.2, 23.3, 19.5)</td>
</tr>
<tr>
<td>Median $pO_2$ during PDT in mm Hg</td>
<td>9.2 (9.5, 50.3, 1.6)</td>
<td>43.0 (52.4, 45.1, 27.6, 37.1)</td>
</tr>
<tr>
<td>Percentage of values ≤2.5 mm Hg pre-PDT</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Percentage of values ≤2.5 mm Hg during PDT</td>
<td>22.1 (0–66.7)</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient B</th>
<th>150 mW/cm²</th>
<th>30 mW/cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median $pO_2$ pre-PDT in mm Hg</td>
<td>25.8 (7.7, 23.9, 36.7)</td>
<td>5.4 (2.7, 4.3, 12.3)</td>
</tr>
<tr>
<td>Median $pO_2$ during PDT in mm Hg</td>
<td>1.0 (0.0, 1.2, 6.0)</td>
<td>21.2 (18.7, 3.7, 30.2)</td>
</tr>
<tr>
<td>Percentage of values ≤2.5 mm Hg pre-PDT</td>
<td>16.7 (3.2–38.9)</td>
<td>19.5 (0–46.2)</td>
</tr>
<tr>
<td>Percentage of values ≤2.5 mm Hg during PDT</td>
<td>54.0 (33.9–76.2)</td>
<td>16.9 (4.1–38.9)</td>
</tr>
</tbody>
</table>

* Number of measured values pre-PDT during PDT.
* Median from pooled data from all lesions.
* Medians from individual lesions.
tion supported by the relatively high oxygen levels in the tumors examined toward the end of treatment. The current treatment light dose of 215 J/cm² may be sufficient to overcome poor efficacy in such a way. The low clinical porphyrin levels compared with those found in mice (6) would enhance the effect of photobleaching, contributing both to efficacy and also to selectivity (20).

Clinical therapies generally seek to minimize treatment times. Although low fluence rates preserve oxygenation, they also prolong illumination (5). However, if PDT efficiency is enhanced, the light dose and treatment time could be reduced. Our results indicate that a large portion of the treatment at 150 mW/cm² must be highly inefficient and treatment time could be reduced. Our results indicate that a large portion of the treatment at 150 mW/cm² must be highly inefficient and suggest that efficiency might be increased at a lower fluence rate. Photochemical oxygen consumption is proportional to the product of photosensitizer absorption coefficient, photosensitizer concentration, and light fluence rate. Photofrin has a relatively low absorption coefficient. Thus, oxygen depletion and therapeutic inefficiency may be even more of an issue for new sensitizers that have much higher absorbances, as well as for topical aminolevulinic acid, which produces high levels of endogenous porphyrin. This study was not designed to evaluate the therapeutic effectiveness of low fluence rate treatment. Additional clinical protocols are being designed to optimize fluence rate and fluence. However, the large interlesion variations in photosensitizer content and baseline oxygenation make it unlikely that one optimal fluence rate can be identified and emphasize the need for noninvasive in situ dosimetry.

Acknowledgment

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References

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