Laser Photoradiation Therapy of Cancer

Anton Dahlman, Alan G. Wile,2 Robert G. Burns, G. Robert Mason, Fred M. Johnson, and Michael W. Berns

Department of Surgery, University of California at Irvine, Irvine, California 92717 [A. D., A. G. W., R. G. B., G. R. M., M. W. B.], and Department of Physics, California State University at Fullerton, Fullerton, California 92631 [F. M. J.]

ABSTRACT

We conducted a trial of photoradiation therapy of cancer at the University of California at Irvine. The basis of this technique is a photochemical reaction between an i.v.-injected material, hematoporphyrin derivative, and red light (wavelength, 630 nm). Hematoporphyrin derivative localized in malignant tissue, resulting in selective destruction of cancer cells upon illumination with red light.

One hundred twenty-eight sites of recurrent cancer or pre-malignant lesions were treated in 37 patients. Of this group, 35 patients had recurrent cancer refractory to conventional therapy, and two had premalignant lesions. Favorable responses were achieved in 67% of the sites treated. The dose of hematoporphyrin derivative used in this study ranged from 2 to 5 mg/kg with the majority of patients receiving 3 mg/kg. Total light dose administered appeared to be the most critical parameter evaluated. Light doses in excess of 20 J/sq cm generally resulted in blistering and necrosis of intact skin, while no appreciable increase in response was observed.

Photoradiation therapy has demonstrable efficacy in cancer therapy and avoids much of the morbidity of current conventional techniques.

INTRODUCTION

The cytotoxic activity of PRT3 is based upon localization of HPD in malignant tissue. Illumination by red light (wavelength, 630 nm) initiates a photochemical reaction which is ultimately lethal to cells. The result is selective tumor necrosis with an extremely high therapeutic ratio.

Figge and Weiland in 1948 demonstrated an affinity of porphyrins for rapidly growing tissues, including sarcomas and carcinomas (5). Selective uptake of hematoporphyrin by tumor cells was demonstrated by Rasmussen-Taxdall in 1955 (11). Gomer and Dougherty confirmed this, using radioactive derivatives of hematoporphyrin ([3H]HPD and [14C]HPD) in the rat (7). It was suggested that optimal tumor concentrations of HPD with minimal amounts of HPD in normal tissues would occur 72 hr following i.v. injection in human subjects.

Techniques for detecting HPD in tumors in vivo were developed by Lipson et al. (10) and by Gregorie et al. (8), based on red fluorescence of HPD when stimulated by UV or blue-green light. This effect was maximal at 3 hr after injection of HPD, being present in 76% of adenocarcinomas and squamous carcinomas as well as in 23% of benign proliferative lesions.

The cytotoxic property of HPD and red light was anticipated by Figge and Weiland in 1949 (6), but successful treatment of human cancer by PRT was first accomplished by Kelly and Snell (9) in a patient with bladder carcinoma. Then, Dougherty et al. (3) in 1978 utilized a xenon arc lamp as the light source in the treatment of a variety of advanced cancers refractory to conventional therapy. A 98% favorable response was reported in this initial effort. Largely through recent basic and clinical research efforts, Dougherty et al. (1-4) and Weishaupt et al. (7, 12) have stimulated considerable interest in photoradiation therapy using HPD.

The intent of the present clinical trial was 3-fold. (a) We attempted to reproduce the favorable clinical responses reported initially by Dougherty’s group. (b) Our second goal was to define the limitations of PRT in terms of morbidity and depth of penetration of the technique. (c) We attempted to optimize the parameters of treatment, seeking maximum tumor response with minimum toxicity.

MATERIALS AND METHODS

HPD. HPD is a derivative of the heme extract, hematoporphyrin HCl, prepared by successive acetylation and hydrolysis. It was supplied as a sterile injectable solution containing 5 mg/ml by Roswell Park Memorial Institute, Buffalo, N. Y. It was stored in the dark until use and was administered by rapid i.v. injections in all patients. Fifty injections were administered to the 37 patients. Eleven patients received a second course of PRT, and 2 of these received a third course. HPD was injected during each course. The amount of HPD was initially varied from 2 to 5 mg/kg, but later in the trial, the dose was standardized at 3 mg/kg. The doses for 41 injections were 3 mg/kg, 6 were 4 mg/kg, 2 were 2 mg/kg, and one was 5 mg/kg.

Light Delivery System. An argon laser (initially Model 164; Spectra Physics, Mountain View, Calif., then Model 171) was used to excite a circulating dye laser (Spectra Physics Model 375 with the tuning wedge removed). Rhodamine B was utilized as the lasing medium (0.79 mg/ml; Exciton, Inc., Dayton, Ohio). The system produced a continuous red beam of light (wavelength, 625 to 640 nm) which was focused onto a 400-μm quartz optical fiber (Math Associates, Inc., Port Washington, N. Y.) by means of an alignment device (Spectra Physics). Output power (intensity) at the end of the optical fiber could be adjusted to a maximum of 1000 milliwatts, as measured using a calorimeter (Spectra Physics Model 404). The output spectrum was periodically checked, using a JY 5-354 monochromometer. The light-emitting end of the optical fiber was supported mechanically, such that the light beam was as nearly perpendicular to the tumor surface as possible. In 3 patients, the optical fiber was passed through the biopsy port of an endoscope, and in another 3 patients, the optical fiber was introduced into the substance of the tumor through the lumen of a 14-gauge needle. The beam diverged gradually, illuminating an area of 50 sq cm at a distance of 25 cm, so tumor sites of varying size could be treated with similar intensity by reducing laser output as the beam was brought closer to its target. Also, sites could be treated with various total light doses depending on exposure time. Intensity of the light at the tumor surface was calculated by measuring intensity of the light emanating from the end of the fiber and dividing this number by the area treated in sq cm. These measurements resulted in an approximation, since they did not take into consideration subsequent scattering by tissue.

1 Supported in part by Grants NIH RR01192, GM23445, and HL15740.
2 American Cancer Society Junior Faculty Fellow. To whom requests for reprints should be addressed.
3 The abbreviations used are: PRT, photoradiation therapy; HPD, hematoporphyrin derivative.
4 Received June 10, 1982; accepted September 29, 1982.
and inhomogeneities of the tumor surfaces. Total light dose was then calculated as the intensity in watts/sq cm multiplied by the treatment time in sec. Thus, intensity is expressed in milliwatts/sq cm and total light dose in J/sq cm.

**Patients.** Thirty-seven patients were enrolled in the clinical trial between May and December, 1981. They had a broad range of malignant and premalignant lesions (Table 1). Twenty-six patients received a single course of PRT, which was defined as injection of HPD followed by light treatments on the third, fourth, or fifth days after injection, with subsequent follow-up for at least 30 days. Illumination with red light was planned for the third day following injection of HPD with additional areas to be treated on the fourth day. Two patients were treated on the fifth day because of time constraints. Nine patients underwent 2 courses, and 2 patients underwent a total of 3 such courses. Three patients received injection and light treatment while hospitalized, and the remainder were treated as outpatients.

Treatment response was assessed by direct measurement of tumor dimensions and was also photographed whenever possible. Follow-up examinations were generally conducted at intervals of 1, 7, 14, and 30 days after light exposure. Subsequent follow-up has been obtained for all patients. Tumor response at 30 days was judged as: complete response, disappearance of all gross tumor; partial response, at least 50% decrease in the product of the maximum cross-sectional diameter of the tumor; stable disease, less than a partial response but not more than a 20% increase in tumor size; or progression, more than a 20% increase in tumor size over the 30 days. The response of adjacent normal tissue was recorded. It was described as no response, erythema, blister formation, or necrosis.

The patients were advised of the experimental nature of PRT. They were told that the purpose of the trial was to develop a new technique for local control and that no treatment of systemic disease was intended. Patients with invasive cancer were entered only after failure of conventional modes of therapy that are known to be effective. They signed a consent form describing our protocol, which was approved by the University of California at Irvine Human Subjects Review Committee. Patients were cautioned verbally and in writing to avoid direct sun exposure during the month following injection of HPD in order to avoid phototoxicity.

**RESULTS**

Of the 128 sites treated, 67% responded favorably. The 2 largest groups, those with local recurrences of head and neck squamous cell carcinoma and those with chest wall recurrences of breast cancer, responded favorably in 85% (12 of 14) and 70% (48 of 68) of sites, respectively. A 42% response rate for cutaneous metastases of squamous cell carcinomas was achieved in a group of patients with large exophytic or ulcerated tumors.

Except for the 2 patients with premalignant lesions, all other participants were considered failures of conventional therapy, including surgery, radiation therapy, chemotherapy, and hormonal manipulation as appropriate. Included in our overall results (Table 1) are 17 treated sites in which the total light dose (in retrospect) was not optimal. Excluded from our overall results are the 4 patients who underwent concomitant chemotherapy in whom the response rate was 93%.

Data were also collected regarding the time interval from injection of HPD to light treatment. Of the 50 courses of PRT, 41 included light treatments on a single day, either the third, fourth, or fifth day after HPD injection. Nine of the 50 courses included light treatments on a combination of the third and fourth or fourth and fifth days after injection. There was no significant difference in response by treatment day (Table 2).

The numbers of patients receiving various doses of HPD were too small to analyze as a separate parameter of therapy. However, early in the trial, it became apparent that favorable responses were frequently observed at the lower doses of HPD. Hence, an empiric decision was made to standardize the dose at 3 mg/kg.

The use of the laser as a light source allowed accurate measurement and manipulation of total light dose and intensity. In breast cancer patients, who had mainly infiltrative skin involvement or large open chest wall ulcers, the response was more frequently favorable when the administered light intensity was greater than 20 milliwatts/sq cm and when the total light dose was greater than 19 J/sq cm (Chart 1).

Responses were apparent as early as 24 hr, at which time they were graded for presence of tumor necrosis, formation of a blister, erythema and edema, or no response. However, not

---

**Table 1**

<table>
<thead>
<tr>
<th>Type of lesion</th>
<th>No. of patients</th>
<th>No. of sites treated</th>
<th>CR*</th>
<th>PR</th>
<th>SD</th>
<th>PG</th>
<th>Favorable responses (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermal recurrences of breast carcinomas</td>
<td>9</td>
<td>68</td>
<td>14</td>
<td>34</td>
<td>19</td>
<td>1</td>
<td>70</td>
</tr>
<tr>
<td>ENT tumors, local recurrences (all squamous cell)</td>
<td>12</td>
<td>14</td>
<td>5</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>85</td>
</tr>
<tr>
<td>ENT tumors, cutaneous metastases (all squamous cell)</td>
<td>8</td>
<td>12</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>5</td>
<td>42</td>
</tr>
<tr>
<td>Colon carcinoma, supraclavicular nodes</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cervical carcinoma, vulvar recurrence</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>Carcinoma in situ of vulva, fourth occurrence</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>Basal cell nevus syndrome</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Total evaluable</td>
<td>33</td>
<td>98</td>
<td>21</td>
<td>45</td>
<td>25</td>
<td>7</td>
<td>67</td>
</tr>
<tr>
<td>Patients excluded due to concomitant chemotheraphy</td>
<td>4</td>
<td>30</td>
<td>25</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>93</td>
</tr>
<tr>
<td>Total</td>
<td>37</td>
<td>128</td>
<td>46</td>
<td>48</td>
<td>26</td>
<td>8</td>
<td>73</td>
</tr>
</tbody>
</table>

*CR, complete response (equivalent to eradication of the lesion by the time of evaluation at 30 days); PR, partial response (at least a 50% reduction in the product of the maximum cross-sectional diameter of the tumor); SD, stable disease (less than a partial response but not more than a 20% increase in tumor size); PG, progression (more than a 20% increase in tumor size over the 30 days); ENT, ears, nose, and throat.
Table 2

<table>
<thead>
<tr>
<th>Dose of HPD (mg/kg)</th>
<th>Treatment cycles</th>
<th>Tumor (necrosis)</th>
<th>Blister</th>
<th>Erythema</th>
<th>NR</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PG</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2</td>
<td>7</td>
<td>17</td>
<td>12</td>
<td>39</td>
<td>3</td>
<td>17</td>
<td>40</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>17</td>
<td>17</td>
<td>12</td>
<td>39</td>
<td>3</td>
<td>17</td>
<td>40</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>7</td>
<td>24</td>
<td>12</td>
<td>43</td>
<td>3</td>
<td>21</td>
<td>45</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>7</td>
<td>24</td>
<td>12</td>
<td>43</td>
<td>3</td>
<td>21</td>
<td>45</td>
<td>25</td>
</tr>
</tbody>
</table>

a NR, no response; CR, complete response; PR, partial response; SD, stable disease; PG, progression. For expanded definition of CR, PR, SD, and PG, see Table 1, Footnote a.

DISCUSSION

Efficacy of PRT. Our results are comparable to those reported previously, thus demonstrating that PRT is efficacious in the treatment of advanced cancers. Furthermore, responses have been relatively consistent, depending on tumor histology and morphology. For example, chest wall recurrences of breast cancer exhibited a 94% favorable response rate when intensity was greater than 20 milliwatts/sq cm and when the total light dose exceeded 15 J/sq cm. Lower doses produced only a 62% favorable response rate. Three breast cancer patients have been excluded from our results because their high response rates could have been due to concomitant chemotherapy, although these patients had progressive disease at the time of PRT. Analysis reveals that 22 of the 30 sites treated in multiple injections of HPD, no cumulative effects were noted.

The illumination of the tumor itself was associated with pain during and after treatment in 20% of our patients. Others reported no associated sensation or some mild to moderate itching.

There were no significant complications in our series. One patient received 27 J/sq cm to his larynx, and 2 others had the base of the tongue treated endoscopically, yet there was no evidence of laryngeal edema or other airway problems. Necrosis of tumor at cutaneous sites was treated successfully by local wound care.

Chart 1. The 30-day response of dermal recurrence of breast cancer with respect to the dose rate (intensity) and the total light dose (red light) administered. O, favorable responses (complete plus partial responses); x, unfavorable responses (stable disease plus progression); mW, milliwatts; cm², sq cm. It is apparent that as the total light dose increased, more favorable responses were observed. However, response appeared to be independent of dose rates.

Chart 2. Patients with dermal recurrence of breast cancer were evaluated in terms of skin response with respect to total light dose 24 hr post-PRT. It is observed that total light dose in excess of 20 J/sq cm was frequently associated with blistering and necrosis of skin. cm², sq cm.
these women received adequate intensities and total doses of light such that these responses were no different from women who were not receiving chemotherapy. Any synergy between PRT and chemotherapy will be evaluated in a separate controlled trial.

Patients with bulky, exophytic cutaneous metastases of head and neck squamous cell carcinoma responded less well to PRT. This lack of response may be related to inadequate penetration of the light through these tumors or inadequate blood supply to deliver HPD to these tumors. The fiber implantation technique was attempted in 2 of these patients without success, despite high light doses. This result is in agreement with the investigators who found that a single fiber is able to produce a cytocidal effect in only 10 ml of tissue (12). Thin cutaneous metastases of squamous cell carcinoma generally responded better to PRT. Variables other than tumor thickness (i.e., light intensity and exposure time) were not associated with significant differences in response.

Patients with local recurrence of cancer of the tongue and floor of the mouth responded vigorously to high light intensities and relatively low total light doses. One patient presented to us with a furrowed and immobile tongue due to recurrent tumor after external beam irradiation and interstitial therapy. He was treated with an intensity of 84 milliwatts/sq cm to a total dose of 20 J/sq cm and did not show evidence of response until his 30-day follow-up visit, when his voice and eating patterns had improved and when his tongue revealed no visible or palpable tumor. Six months later, there was still no evidence of residual carcinoma, and he had gained 21 lb. The only patient who exhibited progression of disease in this group was the second patient treated in our series. An endoscope was not used to visualize this base-of-tongue lesion which, in retrospect, was not illuminated well enough to produce a response.

Morbidity and Limitations of PRT. Although all patients were cautioned to avoid direct and indirect sun exposure, 5 of the 50 injections of HPD (4 patients) were associated with moderate to severe sunlight reactions. In all but one case, these reactions occurred during the first week postinjection, and the patients believe that the reactions could have been avoided by stricter adherence to our recommendations.

Twenty % of our patients experienced pain in the area exposed to the red light. This pain varied from mild to marked in level of intensity. This pain was transient in nature, lasting 1 to 5 days, and was usually controlled with p.o. analgesics.

Most of the patients in our series had had radiation therapy in excess of the levels that would permit adequate wound healing if surgery had been necessary. This was particularly true in 4 patients with cutaneous metastases of squamous cell carcinomas of the head and neck and in 3 patients with recurrent breast cancer, all of whom had large open malignant ulcers or chest wall abscesses. Yet all of these patients demonstrated the capacity to heal these wounds after responding to PRT. Healing was unsatisfactory in areas where tumor persisted after PRT.

Treatment Parameters. PRT has not been well standardized. Efforts to further purify HPD, which appears to be made up of many different porphyrins, are underway as are efforts to obtain more complete data on the pharmacokinetics of HPD in human cancer patients. Use of purer forms of HPD and better timing of therapy could further improve the selective tumoricidal activity of PRT.

In order to evaluate the effect of light in terms of total light dose and dose rate, we have utilized a laser as the light source. This laser light source has allowed precise measurements of these parameters. We have been able to demonstrate a predictable response of tumor and adjacent normal tissue as a function of total light dose. We have also demonstrated that infiltrating neoplasms will respond completely without any more than slight edema in surrounding tissues at the time of therapy, an observation of particular importance for the treatment of lesions in airways or in the alimentary canal.

PRT is clearly more effective in thin, infiltrative lesions than it is in large exophytic tumors. In fact, its selectivity can be expected to allow treatment of large areas around small, early tumors with eradication of any microscopic residual disease. We therefore are implementing further protocols at the University of California at Irvine in order to evaluate the efficacy of PRT in selected early carcinomas.

The data from the clinical trial of PRT at the University of California at Irvine indicate that, in appropriate situations, the treatment is effective and has minimal associated morbidity. We have optimized the various parameters of treatment so as to achieve tumor necrosis with sparing of surrounding normal tissue. The data support future use of PRT as a primary or adjunctive means of therapy for selected early neoplasms.

REFERENCES

1. Dougherty, T. J., Gomer, C. J., and Weisshaupt, K. R. Energetics and efficiency of photoactivation of murine tumor cells containing hematopor-

---

Table 3

<table>
<thead>
<tr>
<th>Interval (days) between injections of HPD to light</th>
<th>24-hr response</th>
<th>30-day response</th>
<th>Favorable responses (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of sites</td>
<td>Tumor necrosis</td>
<td>Blister</td>
<td>Erythema</td>
</tr>
<tr>
<td>3</td>
<td>89</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>34</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Totals</td>
<td>128</td>
<td>24</td>
<td>12</td>
</tr>
</tbody>
</table>

* NR, no response; CR, complete response; PR, partial response; SD, stable disease; PG, progression. For expanded definitions of CR, PR, SD, and PG, see Table 1, Footnote a.
A. Dahlman et al.

Laser Photoradiation Therapy of Cancer


Updated version

Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/43/1/430

E-mail alerts

Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions

To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.