Photodynamic Therapy in Head and Neck Cancer

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Introduction
Photodynamic therapy (PDT) has been actively investigated in various clinical trials since 1988. This therapy has been approved for clinical treatment in the United States, Canada, the European Union, and Japan for several oncologic indications, including obstructing and early carcinomas of the esophagus, stomach, and tracheobronchial tree and recurrent bladder carcinomas [1,2•]. This therapy has also been approved in the United States for treatment of macular degeneration and actinic keratosis. Extensive clinical trials have found excellent results with PDT for basal and squamous cell carcinomas of the skin and Barrett’s esophagus [3,4]. In addition, clinical trials have found PDT to be highly effective in the curative treatment of early and recurrent carcinomas of the head and neck, including the oral cavity, pharynx, nasopharynx, skin, and larynx.

The method of PDT involves use of a photosensitizing agent that is relatively selectively concentrated in abnormal or neoplastic cells. Depending on the type of photosensitizer, it may be injected intravenously, ingested orally, or applied topically. After the photosensitizer is applied, it is relatively selectively retained by tumor cells so that after several hours to days (determined by the kinetics of the compound’s distribution) the neoplastic tissue contains more sensitizer than does normal tissue. The photosensitizer is then activated with a specific wavelength of light that matches the absorption characteristics unique to that specific photosensitizer, usually by use of a laser. This results in tumor necrosis via several mechanisms, including oxygen radical production and vascular shutdown to the tumor. Because the adjacent normal tissue contains less sensitizer, only the neoplastic tissue necroses and the normal tissues are preserved. The advantage of PDT over conventional therapies—surgery, radiation, and chemotherapy—is that it is minimally invasive, lacks systemic toxicity, and results in selective tumor destruction with normal tissue preservation. This advantage is of particular importance for cancer of the head and neck, in which excessive tissue loss leads to significant functional debilities. In addition, because this is an entirely different process, the use of chemotherapy, ionizing radiation, or surgery does not preclude the use of photodynamic therapy. In addition, unlike ionizing radiation, repeated applications of the photosensitizer and activating light treatments can be performed indefinitely.

Photosensitizers
Photodynamic therapy requires three ingredients: a photosensitizer, a light source, and oxygen. The ideal photosensitizer is highly selectively retained by tumor cells; is activated at a long light wavelength, which increases tissue light penetration; and has no side effects.

Photofrin (dihematoporphyrin ether; Axcan pharma, Mont Saint-Hilaire, Quebec) is the most extensively studied and clinically used photosensitizer to date. More than 10,000 patients with various types of cancer have been treated with Photofrin. This photosensitizer is injected intravenously; usually 48 hours after infusion, the tumor tissue is activated at 630 nm of light. Photofrin is relatively selectively retained by cancer cells because of unknown mechanisms. Tumor cell death is caused by oxygen radical production and tumor microvascular shutdown, as well as an undefined immunologic mechanism most likely due to an intense inflammatory response [5•]. The major side effect of Photofrin is skin photosensitivity that lasts up to 6 weeks after infusion. Patients must remain out of daylight for that period [5•,6]. Another limitation of this photosensitizer is the wavelength of light used to activate it. A wavelength of 630 nm penetrates 0.5 to 1.0 cm into tissue. Therefore, larger solid tumors cannot be uniformly illuminated with 630 nm because of limited depth of penetration. As a result of this short light wavelength, Photofrin has limited use in the treatment of large solid tumors.

Several second-generation photosensitizers are being evaluated to improve on some of Photofrin’s limitations.
These photosensitizers include meta tetrahydroxyl phenyl chlorin (mTHPC), benzoporphyrin derivative (BPD), aminolevulinic acid (ALA), tin ethyl etiopurpurin (SnE2), lutitium texaphyrin, and taporfin sodium (Npe6) (Table 1). Foscan (mTHPC, Scotia Pharmaceuticals, Stirling, UK) is the most potent second-generation photosensitizer [7]. It is 100 times more active than Photofrin in animal model studies. The agent is activated at 652-nm wavelength light, with depth of penetration of at least 1 cm [8]. The ratio of tumor to normal tissue concentration is 20:1 in animal studies [9]. Extensive large multinational, multicenter trials using mTHPC-mediated PDT to treat early or recurrent oral carcinomas and for the palliative treatment of refractory oral carcinomas have just been completed. On the basis of these trials, mTHPC has been submitted to the US Food and Drug Administration (FDA) for approval of palliative treatment of refractory or untreatable head and neck cancer. The agent is also in phase II trials in Europe for lung and gastrointestinal tumors.

Vertiporfin (BPD) is an intravenously administered photosensitizer activated with 692 nm of light 3 hours after infusion. It is rapidly cleared and therefore has very limited skin photosensitivity that lasts 1 week or less [10,11]. It is currently in phase I clinical trials for skin and hematologic cancer [12,13]. Vertiporfin also has a higher wavelength of activation, resulting in deeper tissue penetration of light. It has not been evaluated for the treatment of head and neck cancer. Vertiporfin has been approved by the FDA for the treatment of macular degeneration.

The third agent, ALA, is an intrinsic photosensitizer. It has no photosensitizing properties but is converted in situ to a photosensitizer, protoporphyrin IX. The exact rate of protoporphyrin IX accumulation in any tissue depends on metabolic turnover and the capacity of the cell line for heme synthesis. Cancer cells and gastrointestinal mucosa accumulate protoporphyrin IX more actively than do normal cells. This differential synthesis of protoporphyrin IX in cancer cells provides the basis for selective cancer treatment with ALA.

Administration of ALA can be topical [3•], oral [14•], or intravenous. Topical ALA has been used to treat basal cell and squamous cell carcinomas of the skin, with cure rates up to 90% [3•,15]. The agent has been approved in the United States for treatment of actinic keratosis. Oral ALA has been used to treat a small series of patients with oral cancer in the United Kingdom, with limited success [14•]. The drawback of ALA for treating oral cancer is the limited depth of ALA accumulation, which occurs only in the mucosa itself. In addition, oral ALA ingestion results in transient liver function abnormalities that may last up to 1 week after ALA ingestion [14•].

ALA is activated at 635 nm of light, with peak tumor fluorescence occurring 3 to 5 hours after administration. It is rapidly cleared from the body, and skin photosensitivity lasts less than 24 hours [3•]. Because of the limited depth of accumulation of ALA and the limited penetration of 635 nm of light, tumors greater than 2 mm deep are not consistently cured [3•,14•].

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**Table 1. Characteristics of photosensitizers**

<table>
<thead>
<tr>
<th>Sensitizer</th>
<th>Dose</th>
<th>Light conditions</th>
<th>Tumor treated</th>
<th>Optimal time of irradiation, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematoporphyrin derivative</td>
<td>1.5–5 mg IV</td>
<td>630 nm</td>
<td>Clinical: various tumors</td>
<td>24–72</td>
</tr>
<tr>
<td>Benzoporphyrin</td>
<td>4 mg/kg IV</td>
<td>692 nm</td>
<td>MI rhabdomyosarcoma tumor model DBA/2 mice</td>
<td>1–3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50–500 J/cm²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meta-tetrahydroxyphenyl chlorin</td>
<td>0.15–0.3 mg/kg IV</td>
<td>652 nm</td>
<td>Esophageal tumors</td>
<td>36–168</td>
</tr>
<tr>
<td>Aminolevulinic acid</td>
<td>20% topical cream</td>
<td>630 nm</td>
<td>Human mesothelioma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>60 mg/kg oral</td>
<td>40–100 J/cm²</td>
<td>Head and neck tumors</td>
<td>3–5</td>
</tr>
<tr>
<td>Tin ethyl etiopurpurin</td>
<td>1–1.2 mg/kg IV</td>
<td>660 nm</td>
<td>Multiple basal cell carcinoma</td>
<td>24</td>
</tr>
<tr>
<td>Lutitium texaphyrin</td>
<td></td>
<td>732 nm</td>
<td>Metastatic breast cancer</td>
<td>6–24</td>
</tr>
<tr>
<td>Taporfin sodium</td>
<td>1 mg/kg IV</td>
<td>660 nm</td>
<td>Endobronchial cancer</td>
<td>1–6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200 mW/cm²</td>
<td>Metastatic breast cancer</td>
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<td></td>
<td></td>
<td>200 J/cm²</td>
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h—hours; IV—intravenous.