Meta-tetra(hydroxyphenyl)chlorin Photodynamic Therapy in Early-Stage Squamous Cell Carcinoma of the Head and Neck

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Objective: Photodynamic therapy (PDT) is a relatively new treatment modality for various types of cancer, including cancer of the head and neck. The advent of the second-generation photosensitizers such as meta-tetra(hydroxyphenyl)chlorin (mTHPC) (Foscan; Scotia Pharmaceuticals, Stirling, Scotland), which are more effective and less phototoxic to the skin than their forerunners, now makes this treatment a feasible alternative to surgery or radiotherapy in specific cases. To evaluate the long-term outcome of this therapy for squamous cell carcinomas of the head and neck, we treated patients with PDT using mTHPC.

Main Outcome Measure: Complete local tumor remission.

Results: The mean follow-up of the patients after treatment was 37 months. In 25 (86%) of 29 tumors, a complete remission of the primary tumor was obtained. In the 4 recurrences, salvage was achieved by conventional therapy. In none of the patients was any long-term functional deficit detected.

Conclusions: This study confirms that PDT is a powerful treatment modality that could be considered as an alternative to surgery or radiotherapy in specific cases of head and neck cancer. The major advantage of PDT over these conventional therapies is the reduction in long-term morbidity. Radiotherapy or surgery could be reserved for salvage therapy in the event of a recurrence or second primary tumors.

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Squamous cell carcinoma of the head and neck is worldwide one of the major malignancies. Small tumors are conventionally treated with surgery or radiotherapy with equal results. However, even in the treatment of small tumors, surgery and radiotherapy can cause considerable morbidity such as xerostomia, disfiguration, and impairment of important vital functions (eg, swallowing and speech). Initially, photodynamic therapy (PDT) was considered experimental and had only limited applications for some superficially spreading tumors. However, new powerful photosensitizing agents with reduced skin phototoxic effects and improvements in light sources have led to PDT being regarded as a viable clinical alternative to more conventional treatment modalities.

In this respect, meta-tetra(hydroxyphenyl)chlorin (mTHPC) (Foscan; Scotia Pharmaceuticals, Stirling, Scotland) is one of the most potent of the new generation of photosensitizers. This sensitizer has a strong absorption peak at 652 nm, giving better depth penetration of light in tissue than the earlier photosensitizers such as porfimer sodium or 5-aminolevulinic acid, which are activated at lower wavelengths. Only small light doses (10-20 J/cm²) are required to activate mTHPC, which means that treatment times are also much shorter than for porfimer sodium (100-200 J/cm² for effective PDT). Earlier studies have already demonstrated the effectiveness of mTHPC-mediated PDT in different types of cancer. We conducted a prospective study to examine the long-term efficacy of mTHPC in the treatment of early-stage squamous cell carcinoma of the oral cavity and oropharynx.

Methods

Between 1996 and 2000, 25 patients with a squamous cell carcinoma of the oral cavity or pharynx were treated with mTHPC-mediated PDT. None of these patients had a history of other head and neck malignancies. Most patients (68%) had stage I disease, 28% had stage II disease, and 8% had multiple primary tumors. Patient and tumor characteristics are outlined in the Table. All patients were treated according to a protocol approved by the medical ethical committee of the Netherlands Cancer Institute.
tissue. For each illumination, 2 in situ light dosimetry probes to correct for the difference in refractive index between air and played on the monitor. A correction factor of 1.07 was applied for the difference of 15% and were connected to photodiodes with readout electronics. The fluence rate at the tissue surface was dis-

mW/cm² emitted from a 6-W diode laser (Applied Optronics Corp, South Plainfield, NJ) and delivered via a handheld lens fiber (Patrick Thielen Microtechnique, Lausanne, Switzerland). Total light-delivering time and the required distance from the lens to the tumor were calculated based on the total area to be illuminated. The calculated total light dose for all patients was probably much higher than calculated as a result of scattering and reflection of the laser light, in situ light dosimetry was performed on all patients at the level of the tumor surface. 7

Fluence rates were measured using isotropic light detectors. These probes measured total light fluence with an accuracy of 15% and were connected to photodiodes with readout electronics. The fluence rate at the tissue surface was displayed on the monitor. A correction factor of 1.07 was applied to correct for the difference in refractive index between air and tissue. For each illumination, 2 in situ light dosimetry probes were fixed at the edge of the area to be illuminated and in the center of the tumor. Patients were injected intravenously with 0.15 mg/kg of mTHPC dissolved in 30% polyethylene glycol 400, 20% ethanol, and 50% water. Patients then remained in the hospital under restricted light conditions for a total of 7 days.

After 4 days, the patients underwent general anesthesia via nasotracheal intubation in the operating room. The tumor was then exposed by using retractors and/or sutures. Once a clear view of the tumor was obtained, the surrounding tissues were shielded from light by using black copper-wax or dark-colored surgical drapes, leaving an oncological safe margin of approximately 10 mm around the borders of the tumor. Subsequently, the exposed area was illuminated with 652-nm light at a power setting of 100 mW/cm² emitted from a 6-W diode laser (Applied Optronics Corp, South Plainfield, NJ) and delivered via a handheld lens fiber (Patrick Thielen Microtechnique, Lausanne, Switzerland). A total of 25 patients with 29 tumors were treated by mTHPC-mediated PDT. In all patients, necrosis of the illuminated area occurred within 24 hours. This process subsided in all patients within 4 to 6 weeks after treatment. Mean follow-up of patients was 37 months after treatment. In 25 (86%) of 29 tumors, a complete remission of the primary tumor was obtained (Table 1). In none of the patients was any long-term functional or cosmetic deficit detected. The complete remission rate in T1 lesions was 95% vs 57% in T2 disease. This difference was statistically significant (P=.03, χ² test). All cases that developed local recurrent disease were salvaged by surgery and/or radiotherapy. Lymph node metastasis occurred in 5 patients, which was managed by radical (modified) neck dissection in all cases followed by postoperative radiotherapy in 4 cases. One patient died from primary lung cancer.

### RESULTS

A total of 25 patients with 29 tumors were treated by mTHPC-mediated PDT. In all patients, necrosis of the illuminated area occurred within 24 hours. This process subsided in all patients within 4 to 6 weeks after treatment. Mean follow-up of patients was 37 months after treatment. In 25 (86%) of 29 tumors, a complete remission of the primary tumor was obtained (Table 1). In none of the patients was any long-term functional or cosmetic deficit detected. The complete remission rate in T1 lesions was 95% vs 57% in T2 disease. This difference was statistically significant (P=.03, χ² test). All cases that developed local recurrent disease were salvaged by surgery and/or radiotherapy. Lymph node metastasis occurred in 5 patients, which was managed by radical (modified) neck dissection in all cases followed by postoperative radiotherapy in 4 cases. One patient died from primary lung cancer.
Most patients complained of moderate pain in the first days after treatment, which could adequately be managed with analgesics. Four patients developed more serious complications after treatment. One patient, neglecting the postoperative sunlight exposure restrictions, developed second-degree burning wounds on the hands, neck, and abdomen. One patient needed a nasogastric feeding tube for several days because of swallowing complaints. Another patient developed a local inflammation of the forearm after extravasation of a small amount of mTHPC. This complication was well managed by conservative treatment. The fourth patient developed several localized pigmented changes of the skin on the arms after several months. However, a relationship with mTHPC administration could not be established in this case.

Surgery and radiotherapy give good cure rates in early-stage head and neck squamous cell cancer. Surgery requires less time than radiotherapy, and in surgically treated cases radiotherapy can be kept in reserve for recurrent disease and/or second primary tumors. However, excision of even relatively small lesions can result in significant morbidity, depending on the subsite of the primary lesion, because the 1-cm surgical margins (which are mandatory in surgically treated squamous cell carcinoma) may require adjacent structures to be included in the excision. Because of the limited anatomical proportions in the oral cavity and oropharynx, surgical treatment causes anatomical and functional defects, even if structures such as the inferior alveolar process, the tongue, or the soft palate have to be partially resected. Depending on the location and extension of the tumor, the wound may be closed primarily, but in the more extensive tumors the resulting defect must be closed by split-skin grafting or even by pedicle or free flaps. In the head and neck area, surgery therefore often results in cosmetically unsatisfactory scars and can cause considerable morbidity (e.g., speech and swallowing problems).

Although radiotherapy leaves the anatomy intact, it may still lead to important morbidity such as xerostomia and osteoradionecrosis. Furthermore, radiotherapy requires a long treatment period with daily visits to the clinic over 5 to 7 weeks. Particularly for older individuals, this can be overburdening. A major disadvantage of radiotherapy is that it can usually be used only once, leaving surgery as the only salvage treatment (which can cause difficulties in cases of recurrent disease or second primary tumors within the irradiated field).

The present study confirms that modern PDT is an effective treatment modality that should be considered as a possible alternative to surgery or radiotherapy in specific cases of head and neck cancer. The most important functions of the oral cavity and oropharynx are mastication, swallowing, and articulation of speech. None of the patients treated in this series experienced permanent impairment of these functions, which highlights the main advantage of PDT: the absence of the long-term loss of function often seen in radiotherapy and surgery. Photodynamic treatment kills malignant cells but spares the basic cellular architecture. This permits rapid healing after treatment during which the killed cells are replaced by new, normal cells, thereby avoiding the ulceration and fibrosis that commonly occur after other forms of tissue removal.

There was a substantially better response to PDT in the smaller T1 tumors than in the more extensive lesions. Interestingly, all local failures could be treated successfully by conventional treatment such as surgery or radiotherapy. Even among the T2 lesions, a considerable proportion of the patients benefited from PDT in terms of an undisturbed posttreatment anatomy, without scarring or xerostomia. Another advantage for these patients is that they retain the possibility of treatment by radiotherapy or surgery for future events such as second primary tumors.

Although mTHPC is less phototoxic to the skin than the first generation of photosensitizers, patients still have to stay indoors for 1 week after injection and must avoid direct sunlight during the second week. For 3 months after injection of mTHPC, patients should be careful about inadvertent exposure of the skin or eyes to strong light. It is evident that this requires a certain discipline on the part of the patients after they are discharged from the hospital. In just 1 case in the present study, problems were encountered regarding light avoidance. Most patients experienced moderate postoperative pain during the first several days, which could well be controlled by nonsteroidal anti-inflammatory drugs.

In conclusion, PDT is a feasible alternative to radiotherapy or surgery in cases of early-stage squamous cell carcinomas of the oral cavity and oropharynx. An obvious advantage of this new therapeutic modality is that it causes less long-term morbidity than surgery or radiotherapy.

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REFERENCES