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Treatment of primary mucosal head and neck squamous cell carcinoma using photodynamic therapy: results after 25 treated cases

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Abstract

The use of photodynamic therapy for the treatment of malignant and non-malignant conditions is increasing. This paper demonstrates the efficacy of a second-generation photosensitizer, Foscan®, in the primary treatment of a wide range of mucosal head and neck squamous cell carcinomas. Tumours ranged in stage from T_1 to T_3. A complete response to primary treatment was seen in 19/21 patients (90 per cent). In laryngeal cancer recurrent after radical radiotherapy, one out of four patients treated obtained a complete response (25 per cent). Six patients (24 per cent) required surgery after photodynamic therapy, for local recurrence or dysplasia. Mean follow up was for 27.3 months (standard deviation 20.6 months).

Key words: Head and Neck Neoplasms; Photochemotherapy; Treatment Outcome

Introduction

There is a relatively high morbidity and cost associated with standard head and neck mucosal squamous cell cancer (HNMSCC) treatment. Typically, therapy involves a combination of radical surgery, radiotherapy and chemotherapy. Radiotherapy to the head and neck area commonly causes a wide range of debilitating side effects, such as xerostomia, mucositis, loss of taste and loss of smell. These symptoms are often permanent.[1]

Surgical excision and reconstruction can last for many hours, with a consequent increase in general peri-operative complications, along with specific complications such as salivary fistulae, loss of swallowing and loss of speech function. Sometimes there is the need for a permanent tracheostomy. An effective low morbidity alternative treatment is therefore desirable.

Photodynamic therapy (PDT) is a relatively new form of treatment for cancer. It relies upon a unique interaction between light and special chemicals (photosensitizers) to produce free radicals of oxygen at an intracellular level. This causes cell death in a process similar to apoptosis.[2] Of potential advantage is the fact that cancer cells appear to have more photosensitizer inside them than surrounding non-cancer tissue after a specified amount of time has passed (the drug-light interval).[3] The exact mechanisms of this is unknown, but it is quite common to find tumour to normal tissue ratios of drug up to 4:1 in the head and neck region. Thus there can be a degree of selectivity regarding treatment.[4] Laser light delivery is at non-thermal levels. Healing is rapid, as the extracellular matrix is left relatively intact, allowing migration and seeding of normal cells into the spaces previously occupied by malignant disease.[5] This means that post-operative in-patient stay can be minimized, often treatments can be performed on a day-stay basis. Previous studies using first and second-generation photosensitizers have shown very promising results when PDT has been used as a primary treatment modality for HNMSC.[6]

The photosensitizing drug Foscan® has been developed to maximize the efficiency and selectivity of photosensitizing drugs, whilst also having a high absorption peak deep into the red light spectrum, maximizing the penetration of activating light through tissue,[7] hence maximizing the clinical effect.

Material and methods

Foscan® is the trade name of meta-tetra (hydroxyphenyl) chlorin, or mTHPC. It is a second generation photosensitizing drug, with distinct advantages over the most widely used photosensitizing drug, Photofrin® (Table I). Both of these drugs have European regulatory approval for treatment. Foscan® powder is made up into a solution for injection by reconstitution with its solvent (1g

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TABLE I
CHARACTERISTICS OF THE TWO MOST COMMONLY USED PHOTOSENSITIZING DRUGS

	Foscan®	Photofrin®
Unit drug dose	0.15 mg/kg	1.0 mg/kg
Red light peak	652 nm	630 nm
Selectivity	4:1	2:1
Purity	99%	Not possible to measure
Solubility	High	Moderate
Treatment time	200 seconds	1000 seconds

ethanol and 1g polyethylene glycol 400) made up to 5 ml with sterile water for injection. It has a red peak of activation at 652 nanometres (nm); treatment times are usually around 200 seconds depending on the power of the laser and the area to be treated. The drug – light interval is 96 hours for the treatment of HNMSCC. This time interval is felt to give the best conditions for selectivity. (Dilkes, MS Thesis)

Activating laser light at 652 nm was delivered via a variety of laser systems. As diode lasers at this wavelength became available,[8] they were used most frequently, due to their inherent advantages over other sources, such as the copper vapour, KTP pumped tuneable dye laser or gold vapour lasers which we had previously used in PDT treatments (Table II).

In all non-laryngeal cases, laser light at 652 nm was delivered via a calibrated fibre/microlens system. In the larynx, a cylinder diffuser was required to adequately cover the tumour, the light parameters being otherwise the same. Treatment was usually performed under a short general anaesthetic, unless the tumour was easily accessible. The laser light intensity was 100 milliwatts per square centimetre, with 20 joules per square centimetre total light dose delivered, giving a treatment time in all cases of 200 seconds. Normal tissue distant from the laser site was masked with dampened green gauze swabs, or a variety of shielding devices, such as tongue depressors, wooden spatulae etc. A cuff of normal tissue around the tumour was also irradiated, to treat possible submucosal spread. This cuff was usually between 0.5 and 1.0 cm in width. Following irradiation, 8 milligrammes of dexamethasone was administered intravenously in cases where the airway might be compromised (e.g. larynx), to treat any possible swelling. Once the patient was recovered, standard analgesia regimes were instigated. Regular diclofenac and codeine/paracetamol mixtures were supplied for up to two weeks post-treatment. The patient was allowed to go home once any local pain was under control. Patients were extensively cautioned and consented by medical and nursing staff, with particular reference made to avoidance of bright light in the four weeks after injection of photosensitizer.

Results

Twenty-five primary treatments for HNMSCC have been performed using the above protocol, over the past eight years. Twenty-one patients had previously untreated HNMSCC. Four further patients had recurrent cancer after radical radiotherapy for laryngeal squamous cell cancer (Table III). Of the 21 previously untreated patients, 19 (90 per cent) needed no further treatment to the primary tumour site. Two patients later developed neck metastases, which were treated by a combination of functional neck dissection and prophylactic adjunctive radiotherapy. Two patients in the primary treatment group developed recurrent squamous cell cancer in the treatment site. These were treated with surgical excision and adjunctive post-operative radiotherapy. One patient is lost to follow up, the other died of distant metastatic disease 11 months after PDT. Of the laryngeal tumours, three out of four (75 per cent) recurred locally, and required eventual laryngectomy, despite the use of further laser surgery (non-PDT) to try to preserve laryngeal function. Summaries of these results are in Tables III–VII.

TABLE II
COMPARISON OF DIFFERENT LIGHT SOURCES FOR PDT

	Diode laser	Non-diode lasers
Price	round £30 000	Generally over £100 000
Maintenance	Minimal	Complicated systems with high costs
Portability	Excellent – briefcase size, can be used on many sites	Not moveable
Tunability	Not possible, a different laser is needed for each wavelength	Can be tuned across the visible range by use of different dyes
Ease of use	Computer controlled touch screen – easy	Difficult, usually have to be run by a physicist

TABLE III
LARYNX

Patient initials	Site of tumour	Stage of tumour	Follow-up months	Response	Notes
FM	Larynx post DXT	T_2	2	?Complete	Died of lung disease, no tumour in larynx on post mortem
DR	Larynx post DXT	$T_{1/2}$	4	Local recurrence	Further laser excision, laryngectomy
MM	Larynx post DXT	$T_{1/2}$	3	Local recurrence	Further laser excision, laryngectomy
RS	Larynx post DXT	T_2	6	Local recurrence	Laryngectomy
NM	Supraglottic larynx	T_1	2	No residual tumour	Died of heart disease

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TABLE IV
ORAL CAVITY

Patient initials	Site of tumour	Stage of tumour	Follow-up months	Response	Notes
IJ	Oral cavity – premaxilla	Tx	6	Recurrence invading maxilla	Tumour felt to be invading tooth roots – surgery required
FO	Oral cavity	T_2	48	Complete	Condemned mucosa
RB	Oral cavity	T_1	48	Complete	
DA	Oral cavity	T_2	6	Complete	Surgical excision of dysplasia 6 months after rx
WB	Oral cavity	T_2	12	Complete	Condemned mucosa
DC	Oral cavity	T_2	17	Complete	
TF	Oral cavity	T_2	42	Complete	Developed neck metastasis, rx surgery and dxt
JS	Oral cavity – tongue	T_1	12	?Complete	Lost to follow up
WM	Oral cavity	T_3	3	Local recurrence	Surgical resection
RB	Oral cavity	T_3	12	Complete	Oro-antral fistula

TABLE V
OROPHARYNX

Patient initials	Site of tumour	Stage of tumour	Follow-up months	Response	Notes
SY*	Oropharynx soft palate	T2	100	Complete	Developed neck metastasis after 20 months, rx surgery and dxt to neck (not primary site)
DH	Oropharynx	T1	42	Complete	
SY*	Oropharynx soft palate	T1	48	Complete	Second primary on the soft palate, clearly separate from 1st primary
AH	Oropharynx tonsil	T1	40	Complete	Died from oesophageal cancer
JO	Oropharynx – lateral pharyngeal wall	T1	13	Complete	
RB	Oropharynx – hard/soft palate	T3	38	Complete	Oronasal fistula
GR	Oropharynx – soft/hard palate	T3	42	Complete	Developed further disease in tongue base

*Same patient

TABLE VI
HYPOPHARYNX

Patient initials	Site of tumour	Stage of tumour	Follow-up months	Response	Notes
JR	Hypopharynx Pyriform Fossa	T2	15	Complete	Died of 3rd primary and chest failure
RG	Posterior pharyngeal wall	T1	95	Complete	2nd primary oral cavity rx CO2 laser

TABLE VII
NOSE

Patient initials	Site of tumour	Stage of tumour	Follow-up months	Response	Notes
PD	Nose	T1	48	Complete	

DXT = radiotherapy
T = represents tumour in Tumour, node metastasis staging
Complete response = no invasive squamous cell cancer within the confines of the original treatment site at the time of follow-up
Local recurrence = invasive squamous cell cancer within the confines of the original treatment site

Discussion

The results in the primary treatment group for oral cavity, oropharynx and hypopharynx are encouraging and compare well with the standard methods generally used, radical chemo-radiotherapy and/or surgery. The 90 per cent complete response rate also compares well with other published studies using different photosensitizers for this form of treatment. In 1998 Biel found a complete response rate of 89 per cent. Post-operative morbidity was minimal in our series, the treatment sites were usually fully healed within two weeks, and pain was controlled with standard medication, which included patient controlled analgesia for the first 24–48 hours. There was minimal disruption to swallowing and speech function. Quality of life parameters were not measured in all cases, however, it seems unlikely that performance indicators such as the Karnofsky index would generally be affected by this treatment, because of the relatively rapid healing, and lack of functional consequences of treatment. One patient with an extensive oral cavity tumour (patient RB) developed multiple small oro-antral fistulae as a consequence of destruction of tumour invading into

the hard palate. These did not affect swallowing, a covering dental prosthesis was considered but not required.

- **This is a retrospective study of the outcome of photodynamic therapy used in head and neck carcinoma**
- **The patients included are a heterogenous mixture of cases suffering with oral cavity, nasal, oropharyngeal, hypopharyngeal and laryngeal malignancy**
- **The staging varied within the groups and some had previously received radiotherapy**
- **The length of follow up is short in some cases and two patients in the group receiving treatment with photodynamic therapy for oral cavity tumours developed recurrence at the treatment site**
- **This paper suggests that photodynamic therapy will have a role in the treatment of head and neck malignancy**

The two out of 21 primary non-laryngeal cases in which local recurrence occurred were both under staged when the clinical situation was reviewed. Patient IJ had disease recurrence in the tooth sockets, implying previous invasion of these structures prior to PDT. A pre-operative orthopantogram did not show this. Patient WM had a more superficial tumour, but its depth was clearly beyond the scope of PDT. Pre-operative ultrasound might be of help in measuring depth and suitability for PDT.[9] Generally tumours deeper than 5 mm will not completely respond to primary PDT, although initial laser debulking followed by adjunctive PDT to treat the bed may be useful in future.

The main constraint on PDT in terms of the potential for cure after a one-off treatment is depth of tumour from the incident surface of laser light application.[10] Visual access is also important, given that light from the microlens should be delivered with an incident angle as near to 90 degrees as possible. Invasion of non-light transmitting tissue, such as bone, is also a contraindication. For these reasons the most suitable areas for treatment are in the oral cavity and oropharynx, particularly soft palate.

The results of treatment after radical radiotherapy for laryngeal cancer are less impressive. Patients needed airway debridement at least once after treatment, to remove inflammatory slough and dead tissue in the treatment site. The local recurrence rate was high. The fact that these patients had failed a radical course of radiotherapy for their original tumour, and the fact that further ablative laser surgery failed to control their disease, may mean that they had biologically aggressive tumours. This might explain the poor response to treatment. The fact that it is difficult to expose and stage recurrent laryngeal cancer after radiotherapy also mitigates against primary treatment with PDT. It is possible that PDT might be useful in these cases as an adjunct to transoral laser excision, a technique that has since been found to be very useful in this condition.[11] Despite these drawbacks, one patient, who later died of lung disease, appeared to be tumour-free on post mortem analysis. The morbidity from laryngectomy is so high that it might still be worth trying PDT in combination with carbon dioxide laser excision for recurrent laryngeal cancer on the basis that both treatments together may improve the local control rate, and that other authors[12] have had better results in this area.

The main concern regarding PDT relates to skin photosensitivity and the need to avoid bright sunlight for between two and four weeks post treatment. Patients need to understand their instructions regarding precautions taken, and comply with these. In the last three years we have been able to supply light meters to patients, so that they can measure ambient light, and be aware of exposure to dangerous levels. In the series described, one patient failed to adhere to the instructions given, and had to be re-admitted with partial thickness burns to the face and chest. After adequate nursing care, these areas healed without scarring. There were two more cases of more superficial photosensitivity reactions; no specific treatment was required for these.

One of the advantages of PDT in the treatment of primary mucosal head and neck squamous cell carcinoma is that the options of surgery and radiotherapy are held in reserve. A small series of these patients were first reported in 1995,[13] this current much longer follow up demonstrates how the need for further treatment to the primary site has usually not been required, allowing other treatments, in particular radiotherapy, to be used on adjacent sites. These might have been in the original treatment area, and since radiotherapy is cumulatively toxic, they would not have been treatable using this modality. For younger patients, the ability to treat without radiotherapy is particularly useful, since it avoids the potential for radiation-induced tumours in later life, and prevents the long-term sequelae which occur after radiotherapy, which are particularly sorely felt in the head and neck area. PDT can also be given recurrrently, at intervals of around four weeks if necessary. This is because there is no cumulative toxicity, unlike radiotherapy. Theoretically, a large tumour could be serially treated until it was in remission. Alternatively, ablative laser debulking followed by PDT to the tumour bed, as an adjunctive procedure might also be effective for larger or difficult to treat tumours.

Summary

The photosensitizer Photofrin® and Foscan® are now licensed for clinical treatment in Europe. There is lower morbidity when treating appropriate tumours with PDT, when compared to surgery and/or chemoradiotherapy. The complete response rates are similar, and there is the ability to re-treat or treat

uncompromised with standard techniques if local recurrence occurs. Prime sites for PDT when treating head and neck mucosal squamous cell carcinoma are superficial looking (around 5 mm depth) floor of mouth, buccal pouch, lip, lateral pharyngeal wall/tonsil, soft palate and posterior pharyngeal wall carcinomas. Future development might lie in adjunctive as well as primary treatment.

References

1 Epstein, JB, Emerton S, Kolbinson DA, Nhu DL, Phillips N, Stevenson-Moore P, *et al.* Quality of life and oral function following radiotherapy for Head and Neck cancer. *Head Neck* 1991;**21**:1–11
2 Agarwal ML, Clay ME, Harvey EJ, Evans HH, Atunez AR, Oleinick NL. Photodynamic therapy induced rapid cell death by apoptosis in L5178Y mouse lymphoma cells. *Cancer Res* 1991;**51**:5993–6
3 Lin CW. Photodynamic therapy of malignant tumours – recent developments. *Cancer Cells* 1991;**3**:437–44
4 Jefferis AF, Chevretton EB, Berenbaum MC. Muscle damage and recovery in the rabbit tongue following photodynamic therapy with haematoporphyrin derivative. *Acta Otolaryngol* 1991;**111**:153–60
5 Barr H, Tralau CJ, Macrobert AJ, Krasner N, Phillips D, Bown SG. Photodynamic therapy in the normal rat colon with Phthalocyanine sensitisation. *Br J Cancer* 1987;**56**:111–8
6 Biel MA. Photodynamic therapy and the treatment of head and neck neoplasia. *Laryngoscope* 1998;**108**:1259–68
7 Berenbaum MC, Akande SL, Bonnet R, Kaur H, Ioannou S, White RD, *et al.* Meso-Tetra (hydroxyphenyl) porphyrins, a new class of potent tumour photosensitizers with favourable selectivity. *Br J Cancer* 1986;**54**:717–25
8 Dejode ML, McGilligan JA, Dilkes MG, Cameron I, Hart PB, Grahn MF. A comparison of novel light sources for photodynamic therapy. *Lasers Med Sci* 1997;**12**:260–8
9 Souquet JC, Napoleon B, Pujol B, Keriven O, Ponchon T, Descos F, *et al.* Endoscopic ultrasonography in the preoperative staging of esophageal cancer. *Endoscopy* 1994;**26**:764–6
10 Bonnet R, Bernbaum MC. Porphyrins as photosensitisers. In: Bock G., Harnett, S., eds. *Photosensitising Compounds: Their Chemistry, Biology and Clinical Use.* Ciba foundation symposium. Chichester, UK; Wiley; 40–53
11 Steiner W. Results of curative laser microsurgery of laryngeal carcinomas. *Am J Otolaryngol* 1993;**14**:116–21
12 Schweitzer VG. PHOTOFRIN-mediated photodynamic therapy for treatment of early stage oral cavity and laryngeal malignancies. *Lasers Surg Med* 2001;**29**:305–13
13 Dilkes MG, Dejode ML, Gardiner Q, Kenyon GS, McKelvie P. Treatment of head and neck cancer with photodynamic therapy: results after 1 year. *J Laryngol Otol* 1995;**109**:1072–6

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