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Review

The Role of Photodynamic Therapy in the Management of Oral Cancer and Precancer

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Photodynamic therapy (PDT) has promised a great deal in the management of surface tumours for the last 15 years. Why therefore, if it is as good as its enthusiastic supporters claim, has it not become a part of routine clinical practice? Let us critically examine the mechanism of PDT damage. The principles are simple enough: firstly a light sensitising drug is administered systemically. This is retained by tumour tissue with a degree of selectivity so that when the appropriate wavelength of laser light is shone at the tumour, a cold photochemical reaction is triggered with the release of singlet oxygen species and cell killing results. Early enthusiasts claimed the Utopian dream of destruction of tumour tissue with the preservation of adjacent normal structures so that surgeons the world over would be reduced to the role of high street solarium assistants. Much of the delay in development of PDT has resulted from the naivety of such claims. There are, not surprisingly, problems with every step of treatment, starting with the available sensitisers. The most commonly used PDT drug is a haematoporphyrin derivative (or the purified commercially available "Photofrin"). This is well tolerated systemically and is selectively retained by tumour tissue but with tumour to normal ratios in oral cancer of no more than 3:1, this differential concentration cannot be translated into selective necrosis. This does not seem to be a major problem, however, as the connective tissue elements (collagen and elastin) are preserved and act as a matrix for healing without scarring except in muscle. Energy requirements for treatment are of the order of 100 J cm^2, and certainly with early lasers, treatment times could be unacceptably long. There are other effects that make this drug less than ideal, particularly cutaneous photosensitivity which can persist for several months; not a major problem in a grey Northern European winter, but less than desirable in a Mediterranean summer or worse still in the Indian subcontinent, where oral cancer is most common.

Next there are problems with the laser itself. An activation wavelength of 630 nm could until recently only be produced by large and unwieldy dye lasers. These are heavy, expensive, difficult to maintain and at times unreliable, and this fact particularly has caused PDT research to be restricted to a small number of centres; however, using these rather primitive methods it has proved possible to produce consistent full thickness mucosal necrosis and healing without scarring in the mouth [1]. As long as the thickness of the tumour can be established, PDT is the treatment of choice in field cancerisation regardless of the surface area of change [2, 3].

Recent advances in drug development have seen the introduction of new sensitisers. Aminolaevulinic acid (ALA) which is metabolised intracellularly to the active photosensitiser protoporphyrin IX has a very short period of cutaneous photosensitivity (1–2 days) and now has a developing role in the management of cutaneous basal cell carcinomas [4], in particular those arising in the basal cell naevus syndrome. In oral cancer management [5], the superficial PDT effect is more suitable for the treatment of dysplasias and microinvasive disease.

Much greater depths of effect (to about 1 cm) can be gained using metatetrahydroxyphenylchlorin (mTHPC) and trials are under way to clinically evaluate this drug. Although mTHPC can produce prolonged cutaneous photosensitivity and leaves some scarring, treatment times are short (a matter of minutes) and larger tumours can be treated effectively [6].

The problems of cutaneous photosensitivity may be overcome with aluminium phthalocyanine [7] which is due to start Phase I trials later this year. This drug is activated by longer wavelengths of light (675 nm) and there is only limited absorption elsewhere in the visible spectrum, giving the added benefit that the activation wavelength can be generated by diode lasers which are portable, reliable and potentially cheaper than the existing PDT lasers.

The development of safe and reliable PDT has been dogged by enthusiasts, who have not always carried out the basic research required to bring this exciting treatment modality into general use, but it is clear that considerable progress has been made in the treatment of early (thin) squamous cell carcinoma. If the more recent advances in dyes and lasers can

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be translated into practice, PDT should soon play a major role in oral cancer management.

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