CHAPTER FOUR

4.0 CLINICAL TRIALS USING HEMATOPORPHYRIN DERIVATIVE IN CONVENTIONAL PHOTODYNAMIC THERAPY

4.1 Introduction

Clinical use of PDT has been the highest in the United States, Japan, Canada, Australia, China and Italy. The major restriction associated with PDT is the depth of light penetration which in turn limits the size of tumours that can be treated. Interstitial PDT will allow for the treatment of larger tumours, and the continued development of new photosensitizers with better light transmission properties should further improve the depth of PDT-induced tumour necrosis. Transient skin photosensitivity (occasionally lasting more than six weeks after administration of HpD or Photofrin II) remains the primary side effect of PDT. As with most new therapies, the majority of patients treated with PDT have had advanced diseases who either are deemed not suitable for standard treatment, or who had failed to respond to or whose symptoms had recurred after such treatments.

The actual PDT procedures can utilize either direct surface illumination of laser generated light or interstitial exposure. In general, curative effects have been obtained in cases, such as carcinoma-in -situ or early invasive carcinomas of bladder, oral and bronchial mucosa, vagina and skin. On the other hand, PDT is also frequently used for palliation in the case of bulky tumours, including obstructive tumours of the bronchii and oesophagus, as well as for large inoperable tumours. Another promising application of PDT is represented by its combination with the surgical treatment of tumours, with an aim to achieve a better sterilization of the tumour bed. In general, the observation that the previous treatment of the patient with

radio- or chemotherapy does not affect the efficacy or the mechanism of the action of PDT (Dougherty, 1984). The use of PDT is now well established as an adjuvant treatment to radio or chemotherapy for the treatment of a number of forms of cancer.

PDT is useful in cytoreduction and many render large lesions available to surgical excision without need for major surgical reconstruction. Most cancer therapies have disadvantages. For examples, surgery which may be used in breast cancer, is disfiguring and chemotherapy affects the whole body, not just the tumour, but also causing complete hair loss and sickness. The main disadvantage of PDT is prolonged skin photosensitivity although this can be easily controlled by counseling the patients to keep out of sunlight for 4-6 weeks after treatment by PDT.

The treatment of a tumour in a patient by conventional PDT is summarized in Fig.4.1; the basic steps are as follows. The photosensitizing drug in solution is administered usually by intravenous (*i.v.*) injection although intraperitoneal (*i.p.*) delivery has been used in animals. Other possible route of administration might be by oral delivery or by the topical application of the drug in cream or gel base in the case of ALA (amino-levulinic acid). After waiting for an appropriate period (24-48 hrs) of time which depends on the drug used, the administration method and the tumour type, the site of the tumour is irradiated with light, at a wavelength of 630nm (red light). The activated drug then brings tumour cell destruction by processes which have been described earlier in section 2.7.2.

The light dose can be given by surface illumination in the case of superficial skin tumours (eg: squamous cells carcinoma). But for the more deep-seated tumours, an invasive method of light delivery, involving diffusing fibre optics, can be employed.

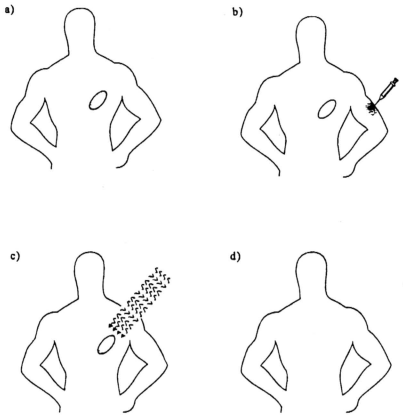

Fig. 4.1 The general procedure for photodynamic therapy:

a) The patient is selected for photodynamic therapy.

b) The patient is injected *i.v* with the photosensitizer

c) After 24-48hrs, the tumour is irradiated with laser light (630nm)

d) The activated drug brings about tumour cell death

A short series of clinical trials had been conducted at the University Hospital of University of Malaya in mid 1993. The existing protocol (Low *et al*, 1988) adopted for clinical trials had been approved by the Ethics Committee of the University Hospital and the drug HpD was also approved by the Drug Control Authority of the Ministry of Health, Malaysia.

The main objective in conducting clinical trials here is to prepare the ground-work to move on to the Hp Immediate PDT clinical programme in the future. Using the conventional HpD-PDT and employing the locally modified light sources, it has been proven to be successful in the first phase of study in treating superficial malignancies. The clinical trials here also served as the basis for endoscopic and interstitial applications for the second phase in clinical trials involving internal malignancies at this centre.

4.2 Clinical PDT For Cancer

4.2.1 Materials And Methods

4.2.1.1 Source Of HpD

Clinical HpD was preprared from commercial HpD following the procedure of Lipson *et al* (1961) as described by Kessel and Cheng (1985a) (refer to section 2.8). All reagents used were of analytical grade. The preparation was conducted inside a Class 1000 Clean Room to ensure the solution is pyrogen free and sterile for intravenous clinical use. Sterility, pyrogen and toxicity test were carried out (refer to section 2.10.4). For each batch of preparation, a random test sampling of 20% of the total number of vials were used.

4.2.1.2 Light Source And Instrumentation

The modified portable surgical head lamp with a fibre optical cable (Schott KL 1500) and the modified filtered red light source based on an overhead projector lamp (Sinon 27A) were used as the light sources for PDT. Both the light sources had a continuous red light with a wavelength of 600-650 nm which coincide with the absorption wavelength of HpD (refer to section 3.5).

4.2.1.3 Patient Selection

The three patients treated had histologically proven malignancies of the skin or breast. The malignant deposits are accessible to an external light beam. For all three cases, other treatment modalities had failed or were found to be unsuitable. The patients were also screened for contraindications including history of allergic conditions (eg. bronchial asthma, atopic eczema, contact dermatitis), sensitivity to drugs, pregnancy and lactation. Informed consent was obtained after providing detailed information on the nature, aims and potential hazards of the clinical trial, particularly regarding skin photosensitivity. Patients were specifically warned to keep away from sunlight and strong roomlight, including fluorescent lamps for a period of 4-6 weeks.

4.2.1.4 Methodology Of Treatment Pre-PDT

Histopathological assessment had been conducted previously to confirm the diagnosis. This was then followed by laboratory investigations which were assessed pre and post PDT. The laboratory investigations were full blood counts, renal function test, liver function tests, plasma

electrolyte levels, blood glucose, ECG and chest X-ray. Clinical HPD that had been stored frozen in darkness was thawed in a beaker of tap water one hour before use. The drug was injected intravenously at a dose of 5.0 mg/kg.

Initially, the patient received a test dose of 1 ml of HPD (5mg/ml) and was observed for 10 mins. With no indication of allergies or other side effects, the remaining dose was given by slow intravenous push. Heart rate and blood pressure was monitored during the administration. Any side effect or anaphylaxis were recorded. The patient was subsequently kept in a dimly lighted room.

4.2.1.5 Treatment Dosimetry

Twenty four hours after the administration of HPD, the patient was given a test dose of therapeutic light of 50 J/cm^2 on a normal skin tissue to assess possible side effects such as erythema or edema. Following the test dose and observation of no response, the lesions were subjected to therapeutic doses of red light, the amount of which depended on the area and the depth of the lesion. Superficial tumours about 3.0 mm in thickness will require a light dosage between 50-150 J/cm^2. During the entire light irradiation procedure, the patients were lying on the bed without any form of anaesthesia. Black cloth masks were used to cover up normal skin tissue. The masks were attached to the skin with adhesive tape throughout the treatment. For treatment on the face, eyes pads were used to protect the patients' eyes from reflected lights. The patients were observed throughout the therapy to monitor for any side effects.

4.2.1.6. Methodology Of Treatment Post PDT

Post treatment changes of the lesions were recorded daily in the first week and subsequently every week for a month. The assessment of response was monitored by tumour volume based on clinical examination, serial photography and biopsy of the site of the treated lesion. The period of histological assessment was at one month and three months and upon recurrence whichever is earlier.

4.3 History and Results Of Clinical Cases

Case 1

A 60 year old woman with a locally advanced right breast tumour involving the skin over the chest bilaterally, the left breast, the axillae supraclavicular lymph nodes were considered for PDT treatment. The tumour was detected more than a year ago but the patient did not seek any treatment. The right breast was practically destroyed by the tumour leaving a large ulcer with a crater like hole in the centre with a depth of 2.0 cm (Fig.4.2). There were many skin nodules (more than 20) over the chest and there was an enlarged fixed lymph node in the right axillae. Large hardened tissue was also palpable in the left breast and the supraclavicular lymph nodes were enlarged. There were no secondaries in the lungs, bones or liver initially. A biopsy in the liver subsequently showed infiltration of ductal carcinoma. She was initailly started on hormonal therapy with tamoxifen at 20 mg daily. On review after a month, there was no improvement seen. She was then started on chemotherapy with the FEC (5 fluorouracil, Epirubicin and Cyclophosphamide) regime 3 weekly. After 2 cycles, no

improvement was seen, and it was decided to try PDT on the patient.

PDT was performed for 60 mins on the large ulcer over the right chest wall with a red light (600-650nm) with effective output power of 1W with a beam diametre of 10.0 cm from the modified filtered projector lamp (approximately 50 J/cm^2). Subsequently another 15 J/cm^2 light was added to the periphery of the ulcer using the modified fibre optic delivery system. Two of the larger skin nodules over the chest wall were also treated using the filtered modified surgical head lamp with 80J/cm^2 and 40 J/cm^2 respectively with a beam diameter of 1.5 cm. Immediately after PDT, edema was seen limited to the large tumour borders. At the same time, small vesicles containing serous liquid was seen oozing out. After 72 hours, the ulcer turned equally black and necrotic. Edema was still present after 3 days. Scab was formed on the nodule which had 80J/cm^2 of light. She was continued on her three weekly chemotherapy regime. After 5 weeks, the centre of the large ulcer was clearing up (Fig.4.3). Thereafter, the wound got smaller in size after 2 months (Fig.4.4). Scab has also fallen off from the small nodule with 80 J/cm^2 of light. The smaller nodule that received 40 J/cm^2 also diminished in size. She remained in this state for 4 months when she was presented with terminal disease due to tumour infiltration into the bone marrow. Her right breast tumour had begun to ulcerate. She succumbed to her advanced metastatic disease.

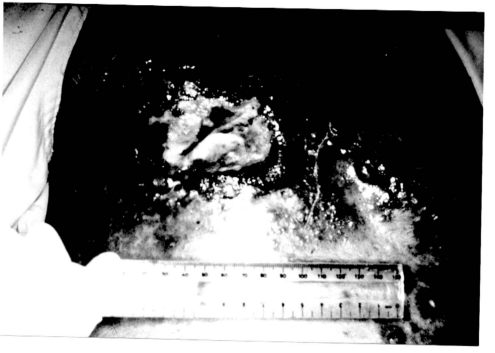

Fig. 4.2 Before treatment

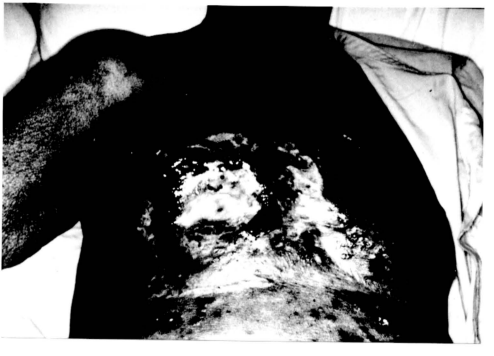

Fig. 4.3 Five weeks after treatment

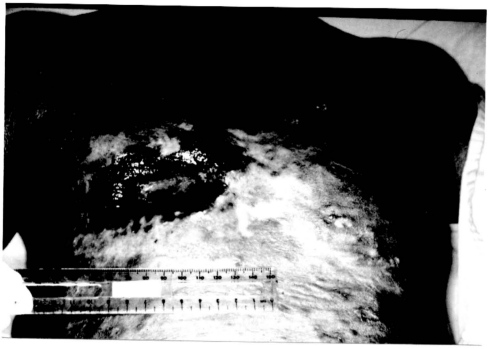

Fig. 4.4 Two months after treatment

Case 2

An 84 year old woman with a non-healing ulcer of the left cheek was also treated. The ulcer was 3.0 by 4.0 cm in size (Fig.4.5) Biopsy showed a well differentiated squamous cell carcinoma and X-rays did not show any bone involvement. No lymph node metastasis were present. She did not agree to surgical excision of the tumour and hence it was decided to treat her with PDT. She was treated using the modified filtered surgical head lamp with a total light irradiation of 100J/cm^2. Tumour necrosis progressed rapidly, initially in areas at the periphery of the tumour lesion and then covering the whole lesion within 3 days of treatment. Fig.4.6 shows the tumour lesion 4 weeks after treatment when the necrotic debris had fallen off and a residual sore was left behind. However, a slightly inflamed area was detected at the lower end

of the original tumour site. This was biopsied and showed residual squamous cell carcinoma. She was then given a second treatment of PDT at the end of one month. Fig.4.7 shows treatment after 2 months; residual tumour remained. After a week, the patient was discharged. She remained well until 2.5 months later when her ulcerating growth started growing back to the original size, she had surgical excision and local flap. Histopathology showed well differentiated squamous cell carcinoma.

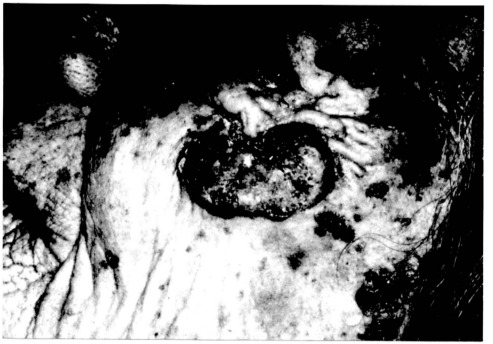

Fig. 4.5 Before treatment

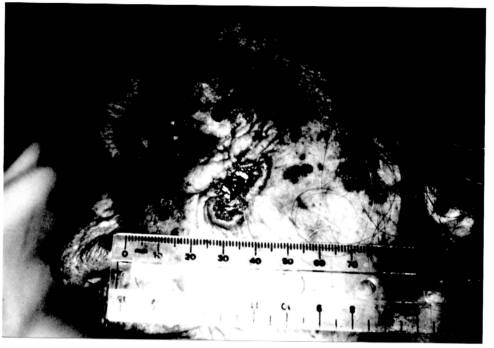

Fig.4.6 Four weeks after treatment

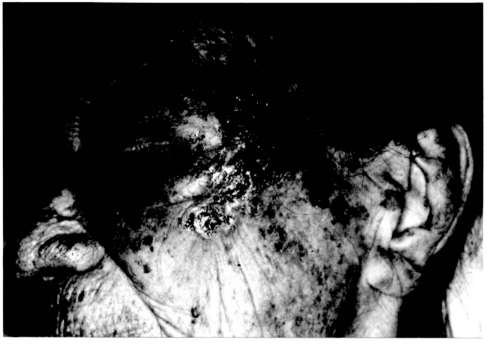

Fig. 4.7 Two months after treatment

Case 3

A 50 year old woman with known Bowen's disease where multiple basal cell carcinoma were found over the face (Fig.4.8) . She had undergone many surgical excisions of the lesions since 1974. On examination, she had multiple pigmented lesions of varying sizes over the whole of her face and neck. Scars from previous surgeries were also present. Seven of her lesions were selected to be treated with PDT. Each lesion was treated using a filtered surgical head lamp with a total light irradiation of $40J/cm^2$. Edema was seen immediately in all treated lesions. She went home after 6 days in the ward. She did not take heed of the advice of staying away from the sun and she returned on the 8th day with severe facial edema, as well as edema over the exposed parts of her hands and feet. She had sustained second degree burns. Photosensitivity was diagnosed and she was started on steriods and antihistamines. Her swelling subsided after 48 hrs. Two weeks after treatment, the lesions had decreased in size (Fig.4.9). However in heavily pigmented areas there did not seem to be much reaction. When reviewed two months later, her lesions had regrown to its original state.

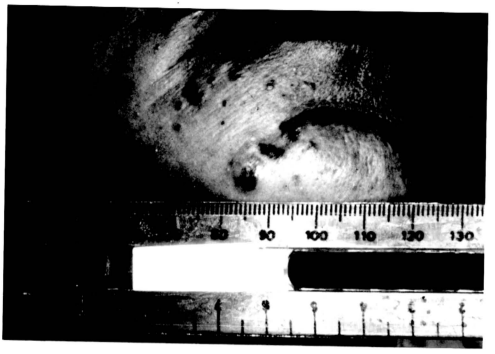

Fig. 4.8 Before treatment

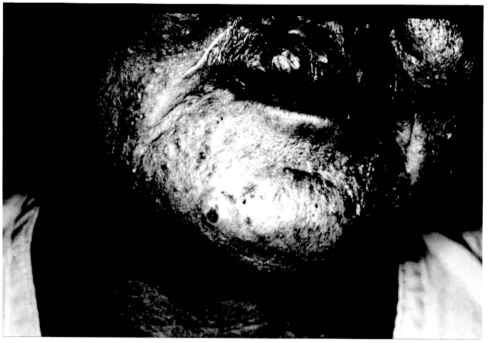

Fig. 4.9 Two weeks after treatment

4.4 Discussion

The cases selected in this initial clinical trial of PDT were patients who had failed to respond to conventional forms of treatment and were in need of palliation or had refused surgical excision.

In all these cases there were definitely positive response of the tumours to HpD-PDT (Chan, H.K. *et al,* 1994). Response obtained were significant in Case 1 (advanced breast tumour). This patient subsequently died after 4 months post treatment. The causes of death was metastatic tumour infiltration into the bone marrow. Nevertheless, due to HPD-PDT, the patient was spared to some extent the distress associated with an ulcerated lesion. Because the treatment of PDT was short in duration, relatively painless and for the main part non-invasive resulting in significant response of the ulcerating wound, there was definite improvement in the well-being of the patient during the months before death.

Case 2 (squamous cell carcinoma) revealed good response but there was residual tumour at the lower edge of the ulcer where there was keratotic skin scab originally. The scab absorbed red light and diminished light penetration into the underlying tumour tissue. However, recurrence occured about two and a half months post PDT. It does appear that keratotic skin surfaces prevent red light from reaching the tumour

Case 3 with basal cell carcinoma, generally showed good respond despite skin photosensitivity. Her second degree burn sloughed off her treated as well as some untreated lesions. The heavily pigmented areas, did not seem to have much reaction. However recurrence occured about 2 months later, which may be because too low an energy density was used in this patient. She declined further PDT for fear of skin photosensitivity.

PDT appears to offer palliative control of the lesions for these patients and all had symptomatic improvement. Although the patients may be mobile, the need to avoid sun exposure limits the patients' activities for at least a month. Keratotic and pigmented skin surfaces also limited light penetration, hampering effective PDT.

Clinical PDT programmes in the treatment of such lesions using simple red light sources should be investigated more throughly in order to obtain better understanding of the basic processes in the PDT of malignancies. Endoscopic PDTclinical trial programmes using laser systems need only be initiated at a later stage in the development of PDT as an alternative modality for the treatment of less accessible malignancies. The modified filtered red light sources appeared to be as effective as laser sources for such PDT treatment of superficial tumours. These simple light sources are attractive alternatives to expensive sources, which are technically more difficult to operate and maintain in a hospital environment.

4.5 Conclusion

In conclusion, the simple light sources here enable much simpler treatment procedures and with a minimum of set-up time. The modified projector light source was highly portable, reliable, inexpensive and focusing devices were built to enable ready adjustment of the beam to a wide range of beam diametres. No hazardous laser irradiation was involved and the patient needs only to be screened from the intense red light beam. The operators need only to wear normal sunglasses to avoid the glare during the light irradiation on the tissue masses.

Low *et al* (1986) and Olivo *et al* (1989) reported that the broad band red output from the halogen projector lamp can be used effectively in animal model works yielding therapeutic

responses similar to that observed using narrow band laser light. Significant therapeutic responses obtained in this work verified further the advantages in using simple red light sources for the PDT of various superficial lesions. The use of such simple red light sources also offered viable PDT procedures for the palliative control of severe advanced external lesions not amenable to surgery and other treatment modalities. The modified surgical headlamp with fibre optic output also enable flexible beam delivery for maneuvering the beam into lens accessible to superficial tumour sites.