PHOTODYNAMIC THERAPY IN THE TREATMENT OF MALIGNANT TUMOURS: AN ANALYSIS OF 540 CASES*

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Summary

Malignant tumours (540 cases), including tumours of the lung, oesophagus, cardia, stomach, rectum, bladder, other urinary genital organs, face and mouth, eyes, ear, nose and throat (ENT), head and neck, breast and skin, were treated using photodynamic therapy (PDT) between 1982 and 1985 in Beijing. All of the cases were identified pathologically and the patients received haematoporphyrin derivative (HPD) (5 mg kg^{-1}) intravenously 48–72 h prior to PDT. An argon-pumped dye laser emitting at 630 nm was used for the treatment. The results were as follows: complete response (CR) was obtained in 227 cases (42.1%), partial response (PR) was obtained in 114 cases (21.1%), mild response (MR) was obtained in 120 cases (22.2%) and 79 cases (14.6%) showed no response (NR). The effectiveness of PDT in the different organs was compared. HPD fluorescence was examined in 409

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cases of malignant tumours: 344 lesions (84.1%) revealed red fluorescence (positive reaction), 32 gave an equivocal response and 33 gave a negative reaction. Positive fluorescence was seen in all types of malignant tumour in our study. Indications and limitations of PDT for the different organs are discussed and compared.

1. Introduction

The clinical treatment of malignant tumours using photodynamic therapy (PDT) has been applied in Beijing since 1980; however, research on the clinical application of PDT in China was started after the establishment of a special PDT study group (the Beijing cooperative hospital experimental laser group) in 1982 [1, 2].

In this paper, we report on 540 cases of malignant tumours which received PDT and 409 cases of malignant tumours which were examined for haematoporphyrin derivative (HPD) fluorescence in the period 1982–1985.

2. Materials and methods

2.1. Patients

409 cases were examined for HPD fluorescence and 540 cases (393 male, 147 female) received PDT. All cases were identified by histological examination before the HPD laser fluorescence test and treatment. In the PDT group, 124 patients (23.0%) were aged between 41 and 50 years and 364 patients (67.4%) were over 51 years.

The various types of tumour examined and treated are summarized in Tables 1 and 2. The pathologic types of tumour included squamous cell carcinoma, undifferentiated carcinoma, adenocarcinoma, basal cell carcinoma, colloid carcinoma, papillary carcinoma, osteoblastic sarcoma, myosarcoma and rhabdomyosarcoma. Most of the patients were inoperable.

2.2. Haematoporphyrin derivative (HPD)

HPD was supplied by the Beijing Institute of Medicine Industry. Skin tests were performed before administration of HPD to ensure that no anaphylactic reaction occurred. If no evidence of hypersensitivity was observed, HPD (5 mg kg^{-1} body weight) was diluted with 250 ml normal saline and injected by intravenous drip 48–72 h prior to laser treatment. The patients were protected from exposure to sunlight for 1 month after injection of HPD to avoid sunburn.

2.3. Light source

An argon ion laser (emission at 488–514.5 nm) was used for the fluorescence tests in most cases. A black lamp (365 nm) and an He–Cd laser (441.6 nm) were also used.

TABLE 1

The results of fluorescence tests on various types of malignant tumours

Location of tumour	*Positive*	*Equivocal*	*Negative*	*Total*
Lung	33	4	3	40
Oesophagus	24	6	5	35
Cardia	41	3		44
Stomach	21	6	1	28
Rectum	9	1		10
Urinary bladder	3	2		5
Other urinary and genital organs	16	1	1	18
Face and oral cavity	93	2	16	111
Eye	12	1		13
ENT	9	1		10
Head and neck	2	1		3
Breast	9	2	1	12
Skin	35	2	1	38
Bone and muscle	25	4		29
Brain	12		1	13
Total cases	344	32	33	409
(%)	84.1	7.8	8.1	100

All types of tumours gave a positive reaction.

TABLE 2

Therapeutic results of PDT on different types of malignant tumours

Location of tumour	*Complete remission*	*Partial remission*	*Mild remission*	*No remission*	*Total*
Lung	9	19	20	6	54
Oesophagus		6	23	14	43
Cardia	3	21	15	9	48
Stomach	2	6	5	3	16
Rectum		9		4	13
Urinary bladder	40	4	4	2	50
Other urinary and genital organs	14		8	3	25
Face and oral cavity	76	15	17	11	119
Eye	10	11	2	10	33
ENT	14	3	2		19
Head and neck	4	3	6	5	18
Breast	7	3	3	1	14
Skin	48	14	15	11	88
Total cases	227	114	120	79	540
(%)	42.1	21.1	22.2	14.6	100

An argon-pumped dye laser delivering a 630 nm beam was used for therapy in most cases. The laser apparatus was built by the Nanjing Electron Tube Factory, the Beijing Institute of Opto-Electronic Technology and the Research Institute of Electronic Technology of the Chinese Academy of Science. Some cases were examined for fluorescence or treated using a Spectra Physics 171-09 argon ion laser and a Spectra Physics 375 B dye laser respectively.

2.4. Fibre optics

Quartz optical fibres (300–400 μm) including flat tip type, lens type and bulb type, were manufactured by the Chinese Institute of Building Materials and the Beijing Institute of Glass Technology or Oncology Research and Development, Inc., NY, U.S.A.

2.5. Methods

2.5.1. Examination of fluorescence

Red fluorescence of HPD in cancer tissue, excited by the argon ion laser or the He–Cd laser, was observed through a brown filter. Lesions in canalized organs were observed through an endoscope; a quartz fibre coupled to the argon ion laser was inserted through the endoscope channel until its tip protruded about 1–1.5 cm from the tip of the endoscope.

The power densities were 50 mW cm^{-2} and 20–40 mW cm^{-2} for the argon ion laser and the He–Cd laser respectively.

2.5.2. PDT treatment

Irradiation was normally performed 48–72 h after the injection of HPD. A power density of 100–300 mW cm^{-2} and an energy density of 100–300 J cm^{-2} were used in most tumours. In the treatment of large tumours, cylindrical fibres were used interstitially. In the treatment of cancer of the lung, stomach, oesophagus, bladder and rectum, the laser beam was transmitted via a quartz fibre inserted through the channel of an endoscope; the flat tip of the fibre was placed approximately 0.5–1.0 cm from the lesion.

According to the number and size of the lesions, multiple exposures were occasionally needed. In the case of bronchogenic carcinoma, after the first treatment, bronchoscopic examinations were performed 1–3 times within the first week to remove debris and necrotic tissues. If there was any residual visible tumour, a second or third laser treatment was given without additional drug. Otherwise, the PDT was assessed 4–6 weeks later for possible re-treatment.

2.6. Criteria of therapeutic effectiveness

The criteria established at the national conference on PDT held in 1984 were as follows: complete remission (the tumour disappears; no cancer cell is found on histological examination for at least 1 month); partial remission (extensive necrosis of tumour; the volume of the tumour decreases by 50%–99% for at least 1 month); mild remission (the tumour volume is

reduced by less than 50% for at least 1 month); no remission (no obvious necrosis; tumour volume reduces slightly or even increases).

3. Results

3.1. Fluorescence of malignant tumours

A positive orange–red fluorescence was seen in 344 out of 409 cases (84.1%). An equivocal reaction was obtained in 32 cases (7.8%), where tumours showed pink fluorescence. A negative reaction was observed in 33 cases (8.1%).

3.2. Therapeutic effect

The therapeutic effect of PDT was assessed on the basis of the necrosis of malignant tumours. After PDT, red and swollen tissues, necrosis and scarring usually occur in superficial tumours, whereas oedema, exudation, necrosis and sloughing of necrotic tissues usually occur in the visceral tumours.

The therapeutic effect was evaluated in 540 cases (Table 2). Complete remission was obtained in 227 cases (42.1%), partial remission was obtained in 114 cases (21.1%) and mild remission was obtained in 120 cases (22.2%). An effective response for PDT was observed in 461 cases (85.4%).

3.3. Side effects

Blood routine, urine routine and hepatic functions examined before and after PDT were normal in this series. Body temperature showed no significant change. The main side effect was allergic dermatitis, which took place in 20 cases after HPD injection and subsequent exposure to sunlight. This was not severe, and subsided within several days. Patients developed pigmentation on their bare skin after the injection of HPD; this usually disappeared within several months. One patient of nasopharyngeal cancer with brain metastasis suffered from vomiting after HPD injection, but this symptom disappeared soon after. These results suggest that the PDT procedure is safe, even in advanced cancer patients.

4. Specific cases

4.1. Case 1

A 75-year-old male complained of dysphagia for 2 months. A tumour with a superficial ulcer was found by endoscope in cardia and identified as cardiac adenocarcinoma. Since this patient also suffered from severe chronic bronchitis and was too old to risk the operation, PDT was performed. After 4 weeks, the symptoms had disappeared and the tumour size had significantly decreased. After 6 months, a second PDT session was performed. The tumour disappeared, no cancer cell was found pathologically, and a normal appearance

was revealed on X-ray analysis 4 weeks after the second PDT. Follow-up for 6 years showed symptom-free, normal, negative tissue in endoscopic and pathological examinations.

4.2. Case 2

A lower lip tumour was identified as a second stage squamous cell carcinoma in a 60-year-old male. After PDT, the tumour disappeared. Complete remission occurred. Follow-up for 7 years showed a normal appearance of the treated area.

4.3. Case 3

A 0.8 cm papillary carcinoma was observed at the orifice of the left ureter of a 42-year-old female; 18 days after PDT, the tumour became necrotic and sloughed off. Complete remission occurred. Follow-up for 20 months showed a normal appearance.

4.4. Case 4

A chest X-ray of a 54-year-old male showed a large tumour located at the left hilum and left lung atelectasia. Fibre-optic bronchoscopy showed an irregular tumour obstructing the left main bronchus. The tumour was identified as an undifferentiated small-cell carcinoma by pathologic examination. X-ray analysis at 12 days after PDT showed that the atelectasia was partially re-expanded. At 1 month, the tumour in the left main bronchus had disappeared. No cancer cells were observed in biopsy specimens. The left lung was entirely re-expanded. The symptoms were significantly improved. However, this patient had metastasis in the mediastinum 7 months after PDT and died due to thrombocytopenia after chemotherapy.

5. Discussion

5.1. Applications of PDT

The effective penetration depth of red light with a wavelength of 630 nm which is used in PDT is to within 1 cm only [3, 4]. Thus PDT can act as a superficial and local method of treatment. It is mainly used for malignant tumours which are inoperable due to various reasons. For malignant tumours of the face, hand, foot and genital organs, operation may bring loss of function or cause aesthetic damage. This technique may be an alternative method for the therapy of malignant tumours and may be more readily accepted by some patients. Advanced cases and cancers of the trachea, larynx and high level oesophagus usually present difficulties for operation. Selective action seems to occur with PDT; it kills tumour cells but leaves normal tissue undamaged [5]. Bladder cancer can also be treated well with PDT; results for superficial bladder tumours are generally good and the procedure is much easier than regular resection [6]. This method can be use in inoperable early stage central-type lung cancer in which the tumour

invades the mucosa of areas that can be reached by the laser beam. PDT can also be used to reduce the extent of resection in order to preserve the function of the organ or improve the general conditions of the patient's airway or oesophageal tract.

5.2. Fluorescence diagnosis of malignant tumours

A large proportion of patients (84.1%) revealed positive fluorescence. This result was improved by using a krypton ion laser instead of the argon ion laser, an image intensifier and a multichannel analyser for the detection of the HPD fluorescence and correction for autofluorescence. If a new photosensitizer could be found with less side effects (*e.g.* one that does not cause skin sensitivity on exposure to sunlight after injection), photodynamic treatment should be widely accepted as an early diagnosis procedure.

5.3. Factors influencing the therapeutic effects

The therapeutic effects vary widely according to the size or stage of the tumours, the extent involved, the location and the methods adopted. Superficial tumours yield better results since they are better exposed to the laser; the mucous exudate and obstruction of the lumen of visceral tumours may interfere with exposure to light. All of the various pathological types of tumours in this study respond to PDT. Different types of fibre optics suit different locations or shapes of tumours. Cylindrical fibres are appropriate for treatment of lesions located on the bronchial or oesophageal wall and for interstitial irradiation of large tumours. The lens-type fibres are suitable for treatment of large tumours during external irradiation. The bulb-type fibre is appropriate for treatment of bladder cancer because lesions usually spread on its spherical wall. The flat tip fibre is very cheap and is suitable for small lesions which can be positioned in front of the tip.

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