Photodynamic Therapy for Residual or Recurrent Cancer of the Nasopharynx

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Abstract

Adequate or effective treatments are not always available for most recurrent or residual nasopharyngeal cancers (NPC). Photodynamic therapy (PDT) using hematoporphyrin derivative (HpD) was evaluated for its effectiveness in treating patients, who conventionally failed, with curative or palliative intent. Thirteen patients were treated from March 1994 to November 1998. PDT was given to eradicate tumor cells, debulk tumor mass for other treatment options, and to resolve obstruction. Long-term tumor control could be achieved in 6 patients with localized lesions at T_1-T_2 stages. The mean disease free survival time was 25.8 months (range 5-61 months). For tumors beyond T_2 stage (7 cases), PDT in combination with chemotherapy, laser surgery or radiotherapy induced complete response in 1 out of 5 patients (survival time = 40 months) and partial response in the rest (survival time = 16-37 months). In two patients who refused or were in tolerable to further treatment, PDT yielded useful palliative results (i.e. resolve nasal obstruction and epistaxis). On an overall basis, the average survival time for these patients with relatively advanced diseases was 24.7 months (range 9-40 months).

Our study demonstrated that HpD-PDT could effectively control locally recurrent or residual NPC at T_1-T_2 stages and offered good palliation for more advanced diseases. Combined PDT and chemotherapy seemed to prolong survival time for a period longer than 2 years in T_3-T_4 tumors.

Key word : Photodynamic Therapy, Nasopharyngeal Cancer Residual Cancer, Recurrent Cancer

Nonresponsive residual disease and a locally recurrent tumor after radiotherapy and combined chemotherapy present a longstanding challenge in the management of nasopharyngeal cancers (NPC)[1,2]. Inaccessibility of the lesion by surgery leaves no option for treatment of the residual tumor. For the recurrent disease, a second course of radiation with doses at least 60 Gy can provide a 5-

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year survival rate of 32-42 per cent in selected patients[3-5]. However, a 10-30 per cent rate of severe complication warrants the need to weigh the expected risk against the comparable benefit in certain cases[3-5]. Alternatively, limited information is available regarding the effectiveness of chemotherapy in the management of recurrent NPC[1,2]. Only cisplatin-based chemotherapy has been reported to achieve a small but constant rate of complete remission (i.e. 13-27 per cent) in a small number of patients[6-9]. The median response duration in most series is unsatisfactorily short, i.e. less than 1 year[6-8]. Longer median survival of 20 months was reported by Chi et al who used a more intensive protocol[9]. Nevertheless, hematologic toxicity leading to significant morbidity and mortality is a major limiting factor particularly for the aggressive treatment protocol[1].

Photodynamic therapy (PDT) is a promising new modality used for treatment of many types of cancers[10]. The treatment concept is rather attractive for a number of reasons[11]. Firstly, it is relatively selective because photosensitive drugs tend to accumulate in cancer rather than in normal tissues and then the drug is activated to kill the malignant cells by laser beaming at the diseased tissue. Secondly, PDT is completely free of the types of complications commonly encountered in radiotherapy and chemotherapy. Thirdly, the treatment can be repeated or used in conjunction with surgery, radiotherapy or chemotherapy. In management of the residual or recurrent NPC with PDT, preliminary results appear quite encouraging[12-15]. Lofgren et al reported long-term tumor control in cases who failed after high doses of radiation[14]. The present study involved the treatment of residual or recurrent NPC with either curative or palliative intent when no other definite treatments were available.

MATERIAL AND METHOD

Patients

Patients were selected according to the following criteria : (a) Recurrent or residual tumor that failed after conventional treatments, (b) refusal or intolerable to conventional treatments, (c) Kanofsky status of 70 per cent or above, (d) normal kidney and liver functions, (e) no evidence of porphyria and pregnancy, (f) good toleration to local or general anesthesia, (g) patients who gave written informed consent. Thirteen patients (9 males and 4 females, age 37-72 years) were treated at Ramathibodi Hospital with an institutionally approved protocol on human rights related to research involved human subjects which is based on the declaration of Helsinki. All patients were referred from the tumor clinic on the basis that the diseases inclined to resist retreatment with radiotherapy. Since all of them had previously received full doses of radiation and chemotherapy. Some were even prescribed with more than one treatment.

PDT treatment

Patients were injected intravenously with HpD (5mg/ml, the Queen Elizabeth Hospital, Woodville, Australia), dosage of 3 mg/kg over a period of 5-10 minutes. They were then advised to stay away from sun light and avoid exposure to bright room light for a period of 1 month to prevent skin photosensitization. At 48-hour post-injection, patients were illuminated under general anesthesia with a 630 nm laser from KTP 532 pumped dye laser system (Laserscope, California, USA). The illuminated area covered at least 0.5 cm beyond the tumor margin. Light dose of 100 J/cm^2 was delivered transnasally by a flat cut optical fiber (400 μm core diameter, Laserscope, California, USA) at on fluence rate of 100 mW/cm^2. The light dose given in 1000 seconds was divided into 4 fractions with few-minute breaks.

Postoperative management and evaluation

Because of its low morbidity[12], PDT was conducted on an outpatient basis. Postoperative management included prescription of analgesic (e.g. paracetamol) and antibiotics (amoxycillin 2 g/day orally for 3 weeks). During 3-6 weeks, the patients were advised to perform nasal douching with normal saline 2-4 times a day. Toilet endoscopy was scheduled weekly for 4-6 weeks.

Degree of tumor response and extent of normal tissue healing were observed while doing toilet endoscopy. Computed tomography (CT) was performed an all patients before and at three months post-treatment. The treated site was biopsied when the CT image suggested a normal finding. A second course of PDT or chemotherapy was given to patients who responded partially. Long-term follow-up was scheduled at 6 months and yearly intervals thereafter. Patients were investigated by CT scan or MRI and endoscopy. Biopsy was performed on patients with a suspicious lesion of recurrence.

The treatment effects were categorized as follows: (a) Complete response (CR): Absence of detectable lesion and biopsy proven negative; (b) Partial response (PR): Reduction by at least 50 per cent in the maximum diameter of the treated area; (c) No response (NR): Reduction by less than 50 per cent in the maximum diameter of the treated area or continued tumor growth.

RESULTS

Characteristics of treatment effect

The treatment effect was immediate. Within 24-48 hours after laser light exposure, acute inflammation was observed at the treated site and rapidly progressed to tissue necrosis and desquamation within the first week post-treatment. Most patients experienced a mild to moderate degree of pain at the treated area. This was relieved by ordinary analgesics (i.e. paracetamol). Crust formation started at the first week and lasted for 2 months. During this time, the patients were scheduled weekly for toilet endoscopy to remove mucous discharge and tissue debris. To combat infection and facilitate tissue healing, they were prescribed antibiotics, antihistamine and decongestants and also taught how to perform nasopharyngeal irrigation. Reepithelialization took place at the sixth week after PDT and continued for a period of 1-1.5 months. In patients who had complete response, the necrotic area epithelialized completely and was not distinguishable from adjacent normal mucosa. For patients who strictly followed safety practice concerning light exposure, side effects of the treatment were extremely mild. Mostly, they experienced skin itching and/or erythema which subsided within a few days without any medication. Skin tanning effect was observed for 2-3 weeks after the treatment and disappeared thereafter.

Treatment outcome

Thirteen patients were treated from March 1994 to November 1998 with a follow-up time of 5-61 months (mean 25.2 months). Among them, eight were cases who had failed even after retreatment with radiotherapy and chemotherapy and five had recurrent cancers (Tables 1 and 2). The patients were divided into 2 groups. Group A (Table 1) included those with local diseases confined to T_1-T_2 stages and the treatment was aimed for cure. Patients whose diseases extended beyond stage T_2 were categorized as group B (Table 2) and were treated for palliation. In this study, up to three courses of PDT were given to relatively advanced tumors at three-monthly intervals with the hope of debulking the tumor for other treatment options. In cases where PDT had failed or yielded only partial response, further treatment with chemotherapy, radiotherapy, or laser surgery was delivered on the ground of patient tolerance or acceptance.

Whether the disease was residual or recurrent, complete response could be achieved for all patients in group A with a single dose of PDT (Table

Table 1. Photodynamic therapy of patients with localized diseases.

Patient	Age/Sex	Disease	Staging before PDT	Histology	Previous Treatment (Initial Staging)	PDT Treatment Number	Response	Duration (month)	Remark Further Treatment	Survival (month)
1	45/M	Residual	T1NoMo	SCC, poorly diff	R+C 1992 (T4 No Mo)	1	CR	61	No	61
2	35/M	Recur	T1NoMo	SCC, poorly diff	R+C 1994 (T3 No Mo)	1	CR	33	No	33
3	43/M	Recur	T2NoMo	SCC, poorly diff	R+C 1988 (T3 N3 Mo)	1	CR	29	No	29
4	72/M	Residual	T2NoMo	SCC, poorly diff	R+C 1994, 1997 (T3 N2c Mo)	1	CR	16	No	16
5	57/F	Recur	T2NoMo	SCC, poorly diff	R+C+S 1991 (T3 N2a Mo)	1	CR	11	No	11
6	37/F	Recur	T2NoMo	SCC, poorly diff	R+C 1996 (T3 N2b Mo)	1	CR	5	No	5

SCC = squamous cell carcinoma; R = radiotherapy; C = chemotherapy ;
S = surgery; PDT = photodynamic therapy; CR = complete response.

Table 2. Photodynamic therapy of patients with relatively advanced disease.

Patient	Age/Sex	Disease before PDT	Staging	Histology	Previous Treatment (Initial Staging)	PDT Treatment Number	PDT Treatment Response (month)	PDT Treatment Duration Treatment	Remark Further (month)	Survival
1	43/M	Residual	T3NoMo	SCC, poorly diff	R+C 1991, 1993 (T3 N2 Mo)	2	PR	6	C (PR, DP for 30 mth)	36 (expired)
2	53/F	Residual	T3N1M1	SCC, poorly diff	R+C 1988, R 1994 (T3 N2 Mo)	3	PR NR, DP	3 6	C (CR, for 31 mth)	40
3	56/F	Recur	T3NoM1	SCC, poorly diff	R+C 1992 (T4 N1 Mo)	1	PR, DP	12	No	12 (expired)
4	62/M	Residual	T4NoMo	SCC, poorly diff	R+C 1990, R 1992, 1994 (T2 No Mo)	2	PR	6	C (PR, DS for 31 mth)	37
5	59/M	Residual	T3NoMo	Adenoid cystic Ca	R+S 1994 (T3 No Mo)	2	PR	6	LS (PR, DP for 17 mth)	23
6	62/M	Residual	T4NoMo	SCC, poorly diff	R+C 1997 (T2 N2c Mo)	3	PR NR, DP	6 8	R (PR,DS for 2 mth	16
7	59/M	Residual	T4NoMo	SCC, poorly diff	R+C 1991, 1997 (T4 N2 Mo)	1	PR, DS	9	No	9

SCC = squamous cell carcinoma; Adenoid cystic Ca = adenoid cystic carcinoma; R = radiotherapy; C = chemotherapy ; S = surgery ; PDT = photodynamic therapy ; PR = partial response ; NR = no response ; CR = complete response; DP = disease progress ; DS = disease stable ; LS = laser surgery.

1). The longest disease free period was 61 months (5.1 years). It was interesting that this long-term survivor was the patient who initially had a relatively extensive tumor with the staging of T_4 N_0 M_0. After receiving full doses of radiation (i.e. 80 Gy to the nasopharynx) and 6 courses of 5-FU and cisplatin, the tumor responded only partially. Successful tumor control was achieved by the use of PDT. All patients in group A are still alive and disease free.

In patients with tumor thickness exceeding 1 cm, i.e. beyond T_2 stage, the treatment yielded only palliative outcomes (Table 2). Nevertheless, all had drastically initial tumor regression as exemplified by Fig. 1. In this group, 2 patients received only one treatment. Because one (patient 3) had distant metastasis, PDT was given to resolve obstruction and epistaxis and the patient expired 1 year after PDT. The other (patient 7) had already received 2 full courses of radiotherapy and chemotherapy and therefore refused to have a second course PDT. With the aim to gain further tumor control, the treatment was repeated for the rest. Although almost all tumors responded appreciably to the second dose of PDT, none of them subjected to complete response. The patients were therefore given six courses of combined 5-fluorouracil and cisplatin to control the disease that might have spread beyond the effective depth of PDT (i.e. 1 cm)[16]. It was interesting that one patient who had a positive neck node and distant metastasis, after having the primary tumor debulked by PDT, responded completely to chemotherapy and is still disease free after nearly 3.5 years (40 months). The rest responded partially. Three are still alive and one expired 3 years after the first dose of PDT.

DISCUSSION

Recurrent or residual tumor in the nasopharynx is the major cause of morbidity and death since no definite treatment has been proven to be effective in patient management[1,2]. Our study confirmed previous reports[13-15] that HpD-PDT was an effective treatment for locally recurrent or residual NPC. In our series, all patients (6 cases) with T_1-T_2 tumors after a single dose of PDT remained disease free for a mean survival time of 25.8 months. The disease is deemed curable since 50 per cent of the patients survived longer than 2 years with no evidence of recurrence. Because of the limited treatment depth ($\leq$ 1 cm) as induced by HpD-PDT[16], partial response could be achieved for T_3-T_4 tumors and maintained for only a short period of time (3-6 months).

Using PDT to debulk tumor mass for chemotherapy was a viable idea. Since long- term tumor control was fulfilled in 1 out of 3 patients treated by this approach. The rest, although responding partially, survived symptom free for more than 2 years. In this study, why did multiple PDT and chemotherapy fail to induce complete response in tumors beyond T_2 stage? Timing for the subse-

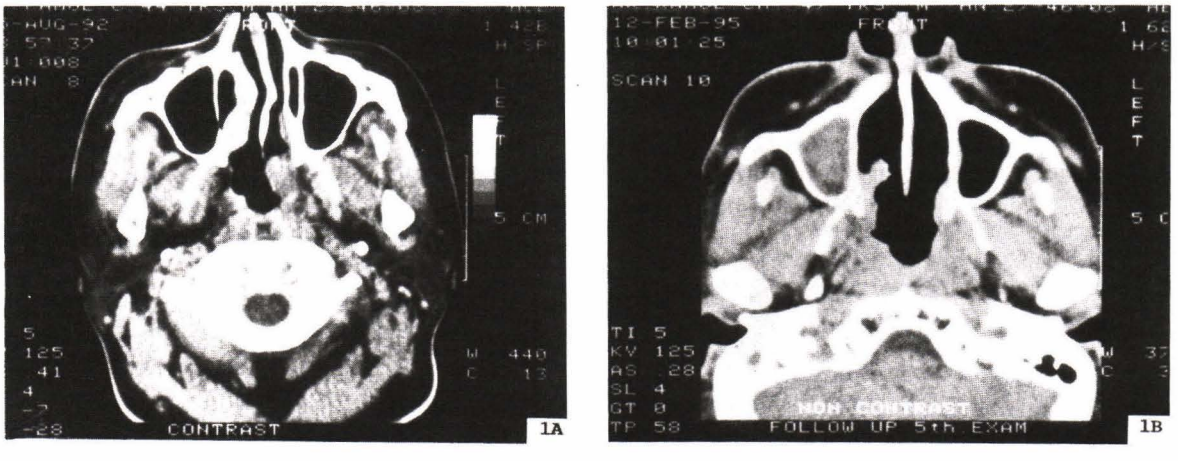

Fig. 1. Tumor response to photodynamic therapy. A. An X-ray computed tomogram showing a residual tumor, diameter 3 cm, extending from left lateral wall of the nasopharynx into the nasal cavity. B. Three months after PDT, the tumor regressed almost completely. The treatment effect was classified as partial response since the treated site yielded a positive biopsy.

quent treatment (three-monthly interval) could possibly be a limiting factor. As a matter of fact, nasopharyngeal cancer is like other cancers in the head and neck for its rapid growth characteristics[1]. Generally, the malignant cells multiply with a median potential doubling time of 4.6-5 days[17, 18]. In radiotherapy, accelerated growth is observed 2-4 weeks after the onset of treatment[19]. In treating relatively advanced disease with PDT, it is likely that the deeper invading malignant cells which escaped photooxidative destruction multiplied progressively during the three -month period to a level too extensive to be controlled by the next dose of PDT. This should explain the cause of failure for multiple PDT observed in this study. Moreover, the disease might even disseminate systemically and thus make it difficult to be controlled by subsequent chemotherapy.

In conclusion, our results strongly support that HpD-PDT continues to be a promising modality in controlling localized recurrent or residual NPC. For more advanced cancers, single rather than multiple PDT might be used as an adjunct to external beam radiotherapy and chemotherapy for two reasons, namely : (a) A single dose of PDT has been demonstrated to be effective in debulking tumor mass. (b) Tumor cells outside the treatment range can multiply rapidly during the three-month period to offset the effectiveness of the second dose of PDT.

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การรักษามะเร็งที่กลับเป็นซ้ำหรือหลงเหลืออยู่หลังการรักษาในบริเวณหลังโพรงจมูกด้วยวิธีโฟโต้ไดนามิค

บุญชู กุลประดิษฐารมณ์, พ.บ., วิภา บุญกิตติเจริญ, ปร.ด.***

การไม่ตอบสนองต่อการรักษาเป็นปัญหาที่พบได้เสมอสำหรับมะเร็งที่กลับเป็นซ้ำหรือหลงเหลืออยู่หลังการรักษาในบริเวณโพรงหลังจมูก งานวิจัยนี้ได้ประเมินประสิทธิภาพของการรักษาวิธีโฟโตไดนามิค (photodynamic therapy, PDT) ในการรักษามะเร็งดังกล่าวเพื่อหวังผลหายขาดและประทังอาการผู้ป่วยจำนวน 13 รายได้รับการรักษาด้วยวิธีดังกล่าวระหว่างเดือนมีนาคม 1994 ถึงพฤศจิกายน 1998 เพื่อกำจัดหรือควบคุมมะเร็ง หรือลดขนาดของก้อนเนื้อร้ายเพื่อให้ง่ายต่อการควบคุมด้วยเคมีบำบัดรังสีรักษาหรือการผ่าตัด ผลปรากฏว่า PDT สามารถควบคุมโรคในระยะต้น (T_1–T_2) จำนวน 6 รายได้ดี ระยะปลอดโรคโดยเฉลี่ยนาน 28.5 เดือน (ระหว่าง 5–61 เดือน) ส่วนมะเร็งในระยะเกิน T_2 (7 ราย) การใช้ PDT ร่วมกับวิธีการรักษาอื่นดังกล่าวข้างต้นสามารถทำลายมะเร็งได้อย่างหมดจดในผู้ป่วย จำนวน 1 ใน 5 ราย โดยมีระยะปลอดโรคนานถึง 40 เดือน ที่เหลืออีก 4 ราย มะเร็งมีขนาดเล็กลงกว่าครึ่งหนึ่ง (ระยะเวลาการอยู่รอดนาน 16–37 เดือน) ในผู้ป่วย (2 ราย) ที่ปฏิเสธหรือไม่อาจต้านทานต่อเคมีบำบัด PDT สามารถบรรเทาอาการหายใจขัดหรือหยุดเลือดกำเดาได้อย่างดี กลุ่มผู้ป่วยที่โรคค่อนข้างลุกลามนี้ มีระยะเวลาการอยู่รอดโดยเฉลี่ยนาน 24.7 เดือน (ระหว่าง 9–40 เดือน)

ผลการวิจัยนี้ได้แสดงให้เห็นว่า PDT ซึ่งใช้อนุพันธ์ฮีมาโตพอร์ไฟรินเป็นยาไวแสงสามารถควบคุมมะเร็งย้อนกลับหรือคงค้างในบริเวณโพรงหลังจมูกในระยะ T_1–T_2 ได้อย่างมีประสิทธิภาพยิ่ง และดีต่อการรักษาแบบประทังในโรคระยะค่อนข้างลุกลาม การใช้ PDT ร่วมกับเคมีบำบัดสามารถยืดชีวิตผู้ป่วยในระยะ T_3–T_4 ได้นานเกิน 2 ปี

คำสำคัญ : การรักษาวิธีโฟโตไดนามิค, มะเร็งหลังโพรงจมูก, มะเร็งที่กลับเป็นซ้ำ, มะเร็งหลงเหลือ

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