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Photochemotherapy Mediated by Hematoporphyrin Derivative in Gastroenterology

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Abstract—*While results concerning photodynamic treatments of cancers in pneumology or dermatology have been published regularly, few works have been devoted to gastroenterology. Twenty-seven non-operable patients bearing various G.I. tumors of less than 40 mm dia. have been treated by PDT for palliative purpose to appreciate the local efficacy of a single treatment. Before July, 1985, the parameters of treatment were 2.5 mg/kg of HPD injected intravenously for theoretical power of delivered laser light (630 mm) 300 mW. After July, 1985, HPD was injected at the dose of 5 mg/kg and the laser dose was 400 mW. A normalization of grip biopsies was observed on 12 patients (6 squamous cell carcinomas, 6 adenocarcinomas), transient in 3 cases.*

Our main finding is that PDT seems able to destroy significant volumes of tumor by itself although subsequent biopsies proved negative in very few cases.

This method remains to be compared to others less sophisticated than the YAG laser.

INTRODUCTION

SINCE its discovery by Maiman in 1960, the laser has been increasingly used for a variety of medical applications, especially in gastroenterology. The Nd–YAG (neodymium-doped yttrium–aluminum–garnet) laser has been the most widely used type in palliative oncology [1, 2] because of its thermic properties. More recently, with the advent of photochemotherapy (PDT), a dye-laser has been used in addition to the other sources. The theoretical principles of this type of therapy are simple and thus attractive. A photodynamic agent, hematoporphyrin derivative (HPD), is injected intravenously and retained selectively by tumor tissue [3]. A specific laser light irradiation is then performed, inducing HPD excitation and leading at the same time to the production of singlet oxygen [4, 5], a toxic, excited form of oxygen. Although results concerning PDT in pneumology [6, 7] or dermatology [8] have been published regularly, few works have been devoted to gastroenterology. In our preliminary study without control subjects, 27 patients were treated by PDT for palliative purposes to assess the local efficacy of this procedure. The results presented here were evaluated both endoscopically (2 operators) and histologically (regular biopsy samples).

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PATIENTS, MATERIALS AND METHODS

Patients

Between May, 1984, and November, 1985, 27 patients (8 women, 19 men) mean age 72 years (45–91 years) were treated for tumors of different histological types localized at various sites along the digestive tract. Of 8 esophagus squamous cell carcinomas, 6 were found in the upper third, 1 in the middle third and 1 in the lower third. They appeared either as a flat ulceration (3 cases) or a discrete irregular raised area (5 cases). All the other cancers were adenocarcinomas localized in the cardia (1 case) or the stomach (8 cases: 6 lesions of the upper part of the fundus, 2 of the pyloric antrum). In the other 12 cases, the tumors were located to the sigmoid (6 cases) or rectum (6 cases), including 1 which was infiltrating and ulcerated.

All these patients presented definite contraindications to surgery owing to metastatic spread or reappearance of the tumor after radiotherapy in 10 cases, or to the existence of associated diseases (severe cardiovascular problems, cirrhosis of liver) in the other cases. The common factor for the lesions in this heterogeneous series was tumor size (between 10 and 40 mm dia., with the exception of 1 case

50 mm dia.) as assessed by comparison with an opened biopsy grip.

Materials and methods

Once the pathology was histologically confirmed and the assessment of the spread of the disease completed, the patients received an HPD infusion of 2.5 mg/kg of body weight before July, 1985, and of 5 mg/kg from July to November, 1985, diluted at 10% (250 cc) in hypertonic glucose serum. HPD was prepared by the Nantes University Hospital pharmacy according to the method of Gregorie and Lipson [9, 10]. The infusion was done in 60 min in total darkness. Laser irradiation was performed 72 hr after the end of perfusion, and patients were kept out of direct light during this period. A Coherent (Palo Alto, CA) CR 599 dye-laser was used, pumped by a Coherent Innova 90 ionized argon laser. The output power at the fiber tip was set (using an L.E.L.T. power meter, Lorient, France) at 300 mW for 632 nm before July, 1985, and at 400 mW between July and November, 1985. The wavelength was measured by comparison with a He–Ne laser by means of a passband filter. A 400 μm (core diameter) silica–silicon optic fiber (Quartz et Silice, France) was used. In 20 cases, irradiation was performed by implanting the tip of the optic fiber directly into the lesion, but in the other 7 cases only external, defocalized irradiation was technically possible. Interstitial irradiation was performed at the rate of one intratumoral implantation per 8 mm and with an exposure time of 5 min per site. The *theoretical* energy density was 150 J/cm^2 in the first procedure (before July, 1985) and then 220 J/cm^2 (determined from experimental measurements on mice, with distance optical fiber–target equal to 60 mm).

Olympus GIF Q endoscopes were used for esophageal and gastric lesions and CFMB3 for lower digestive tract lesions. The follow-up protocol was as follows: endoscopy with biopsies 2 months after irradiation, when PDT-induced lesions are maximal, and then every 2 months. Supplementary Nd–YAG laser treatment or radiotherapy was performed when possible (6 cases), but never before the second follow-up control (PDT + 4 months).

Results have not been expressed in statistical terms because the treatment procedure varied from July 1985, and also because the intratumoral irradiation has not been possible for all patients.

RESULTS

At the time of writing this report, in April, 1986, the post-treatment period has been brief for cases in this series, ranging from 1 to 23 months. Twelve patients presented locally negative biopsies (transient in 3 cases): 7 before July, 1985, and 5 out of 7 after July, 1985 (6 squamous cell carcinomas and 6 adenocarcinomas). When a relapse occured, it happened after a disease-free period of 4 months in 1 case, and a period of 6 months in the other case. Four of these 12 patients have died (3 cancers of the esophagus), but in 2 cases necropsies indicated no tumor tissue at the irradiation site, although metastatic spread was the cause of death of 1 of the 2 patients.

Among the other patients, 11 presented a regression at 2 months in the form of an endoluminal caseous necrosis more than 50% of the size of the initial tumor. In 3 other cases necrosis was also apparent but comprised less than 50% of the initial tumor size. Finally, a total absence of effect was noted in 1 case for which no explanation could be given.

In technical terms it is of interest to note that the optic fiber was destroyed at its distal end during interstitial irradiation at 12% of the sites, which required recutting of the fiber one or more times during the examination. There were no other incidents, and only 1 case of photosensitization occurred, while the patient was being transported by ambulance; all patients had been advised orally and in writing of the risks of over-exposure to u.v. radiation.

DISCUSSION

Therapeutic endoscopy is frequently proposed as an alternative way to surgery for cancer treatment of the GI tract, in non-operable patients. In pneumology and urology, PDT has been used in endoscopy for curative as well as palliative purposes. Until now, few cases of its curative use in gastroenterology have been reported [11, 12].

The series reported here was without controls and heterogeneous with respect to the type of lesions treated, but it serves to show that PDT, based on the use of a photosensitive substance irradiated by a light source, results in significant tissue destruction in most cases. There were only a limited number of negative histologic results.

The follow-up is very short, but it is of litle importance as the aim of the study was to appreciate the endoscopic response to a single PDT session. This relative ineffectiveness of curative therapy was due in part to the absence of data concerning the depth of involvement of the GI tract wall regardless of the organ affected. In this respect, it may be said that local treatment will only play a role in oncology if 2 conditions are met: the development of echo-endoscopy, and of effective regional and general treatment of the cancerous disease.

Variability in the preparation of HPD [13] does not seem to have been a factor accounting for our poor results since the same batch was used for our *in vitro* and *in vivo* experiments which gave results consistent with those in the literature.

Table 1

Patient No.	Type	Lesion diameter (mm)	Loc	Date of treatment	Complementary treatment before relapse	Relapse	Disease-free period (months) last biopsies	Death
3	SCC	20	1/3 S	7/84	—	+	4	+
9	SCC	10	1/3 I	2/85	—	−	1	Necropsy (−)
14	SCC	25	1/3 M	5/85	R*	−	6	Necropsy (−)
15	SCC	10	1/3 M	6/85	Nd–YAG	+	6	−
20	SCC	20	1/3 S	10/85	R*	−	6	−
23	SCC	15	1/3 M	11/85	—	−	6	−
5	ADN	30	20 cm	8/84	R*	−	6	+
17	ADN	25	12 cm	8/85	—	−	8	−
21	ADN	20	10 cm	10/85	R*	−	6	−
25	ADN	35	14 cm	12/85	—	−	4	−
2	ADN	20	Antrum	6/84	—	−	22	−
7	ADN	10	Fundus	11/84	—	+	6	−

The advantage of PDT does not seem to be related to the destructive effect of the method but rather to its relative harmlessness for normal cells due to the fact that HPD is retained selectively [14] by tumor tissues. Moreover, this selectivity has been linked to vascular alterations during the *in vivo* photochemical reaction. Despite the few studies carried out thus far, selectivity seems clearly established *in vitro* in certain experimental models [15, 16].

The mechanism of tissue destruction with PDT remains unclear. Hyperthermia due to laser irradiation enhances the photodynamic reaction mediated by singlet oxygen production [17, 18]. However, at the power used, PDT induces a mild increase in temperature at the border-line level to the one obtained in clinical hyperthermia [15, 19, 20] but for a relatively short time. Thus hyperthermia due to PDT does not seem able to provoke any tissue damage by itself.

The dye-laser would thus not seem to be competitive with the Nd–YAG laser which allows destruction of a considerable intraluminal tumor mass during a short endoscopic act. We even showed that the Nd–YAG laser alone could give a complete tumoral destruction in certain circumstances [21].

PDT should, in fact, be considered as a complementary treatment to thermal debulking to obtain complete tumor remission locally and should thus become an essential element in protocols including radiotherapy, chemotherapy and even hyperthermia [17], a role which would seem quite logical since its use does not contraindicate any subsequent act.

CONCLUSION

Photochemotherapy is a method of treatment based on a simple principle. Our Phase 1 therapeutic study of patients with digestive tract cancers provided encouraging results but also indicated numerous obstacles to the development of this method. The few results published relative to gastroenterology do not allow us to compare our own with those in the literature. It must be considered that the method is quite recent and that much progress remains to be made, both in terms of the photodynamic substances, still limited today to HPD, and of the laser sources which will have to be adapted to such future substances.

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