Adjuvant photodynamic therapy for bile duct carcinoma after surgery: a preliminary study

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Background. Photodynamic therapy (PDT) is a new palliative option in patients with non-resectable bile duct carcinoma (BDC). Here, we assessed the efficacy of adjuvant photodynamic therapy in eight patients with BDC who underwent surgical resection.

Methods. Five patients had extrahepatic BDC, two had intrahepatic cholangiocarcinoma, and one had ampullary carcinoma. Cancer cells were microscopically detected in the stump of the hepatic duct in six patients, and biliary stenosis caused by remnant tumor was observed in one patient. One patient had tumor recurrence with occlusion of the bile duct. At 48h prior to PDT, porfimer sodium was injected intravenously. A pulse laser by an eximer dye laser (50–100 J/cm²) with a wavelength of 630 µm was applied through an endoscope to the hepatic stump or tumor lesion.

Results. Marked destruction of the tumor and ductal epithelium was observed on day 1 after PDT. After PDT, four patients developed mild dermatitis, but no severe morbidity or mortality was noted. In patients who underwent PDT for the stump, one patient showed distant metastasis at 31 months, and four patients did not show tumor recurrence at 17, 12, 12, and 6 months, respectively. However, one of the eight patients died at 2 months, of an unrelated cause. In two patients with occlusion caused by tumor growth, resolution of bile duct stenosis was noted on day 7. These patients showed re-occlusion by tumor at 20 and 8 months.

Conclusions. Adjuvant PDT is a safe and useful option for a better survival benefit in patients with BDC undergoing surgical resection.

Key words photodynamic therapy, porfimer sodium, eximer dye laser, bile duct carcinoma, adjuvant treatment

Introduction

Advances in imaging diagnostic technology in the past two decades have allowed early detection of bile duct carcinoma (BDC).1–3 Accordingly, the number of patients with resectable BDC has increased, and patient survival has improved in recent years.3,4 However, curative resection is often difficult, because BDC spreads extensively along the bile duct beyond the lesion noted at the preoperative diagnosis.4 Positive surgical margins in the stump of the hepatic duct are a significantly poor prognostic feature compared to positive duodenal margin or exposed margin of the bile duct, as reported previously.5 To date, there are no data supporting the survival advantage of adjuvant radiotherapy and/or chemotherapy after surgery for BDC.6,7 On the other hand, for recurrence in the bile duct after surgery, placement of a metallic stent for stenosis has improved quality of life. However, stent occlusion by tumor ingrowth or other causes is frequent, and local ablation therapies have been used for recanalization.8 To resolve these problems in BDC treatment, effective local treatment is necessary.

Photodynamic therapy (PDT), which is a form of laser treatment, has led to remarkable regression of malignant tumors, including BDC, since the 1980s.9 In this treatment, a photosensitizing drug known to accumulate in the mitochondria or lysosomes of tumor cells is intravenously administered, and the photosensitizer, activated by laser light of the appropriate wavelength, forms a cytotoxic reaction in cancer cells or neovascular cells surrounding tumors.9 At present, PDT is used for superficial cancers or premalignant lesions in the upper digestive tract, lung, cervix, or skin, and the cost for these purposes is covered by national health insurance in Japan.10 In the latter half of the past decade, several investigators have reported the clinical usefulness and survival benefits of PDT for non-resectable BDC in a randomized multicenter trial.11–14 Subsequently, Berr et
al.\textsuperscript{15} and Wiedmann et al.\textsuperscript{16} recently reported the usefulness of PDT as a neoadjuvant therapy for resectable BDC. Thus, PDT is also apparently a useful modality for local treatment in BDC.

In the present study, we describe our experience using PDT as an adjuvant local treatment to control remnant tumor in the hepatic duct stump after surgical resection, and to place metallic stents in severely obstructed bile ducts after surgery. We report here the short- and long-term clinical effectiveness and outcome after PDT.

**Patients and methods**

**Patients**

The subjects were eight patients with extrahepatic or intrahepatic BDC who were admitted to the Division of Surgical Oncology, Department of Translational Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences (NUGSBS), Japan, between May 2001 and January 2004. The mean age of the patients at the time of surgery was 64.0 years (range, 55–69 years), and there were five men and three women. Prior to surgery for cholangiocarcinoma, the patients had been treated with percutaneous transhepatic biliary drainage (PTBD) to alleviate obstructive jaundice, but none had received chemo- or radiotherapy. None had any other major disease and all had good performance status before surgery and PDT. Tumors were assessed by computed tomography (CT) scan, magnetic resonance imaging cholangiography (MRC), cholangiography or cholangioscopy (via drainage tubes), or intraductal ultrasonography (IDUS; 20 MHz).

The surgical procedures comprised extended left or right hemihepatectomy, with total resection of the caudate lobe and resection of the extrahepatic bile duct, or pancreaticoduodenectomy. Resections were performed en bloc, based on the preoperative imaging diagnosis; lymph node dissection was performed on the hepatoduodenal ligament, surrounding pancreas head, and paraaortic lesions. All hepatic tumors were resected without macroscopic exposure of the amputated section; however, microscopic infiltration of cancer cells was diagnosed by pathological examination during and after surgery. Complete resection failed, requiring additional resection of the hepatic duct in five patients, or failed because of poor hepatic function in two. We used the Classification of biliary tract carcinoma\textsuperscript{17} and the General rules for the clinical and pathological study of primary liver cancer.\textsuperscript{18} We referred to the Bismuth-Corlette classification for hilar bile duct carcinoma.\textsuperscript{19} The study design was approved by the Ethics Committee of NUGSBS, and signed consent was obtained from each patient before the procedure. As PDT for bile duct carcinoma is not covered by the national health insurance scheme in Japan, the National Expense for Special Research Programs at NUGSBS was used for medical expenses associated with PDT in all patients.

**Photodynamic therapy**

All patients who received PDT were in a stable condition, based on physical examination and laboratory tests after operation or biliary drainage (mean ± SD; 29 ± 13 days, ranging 21 to 41 days). Porfimer sodium (Photofrin; Wyeth Pharmaceuticals, Collegeville, PA, USA, and Wyeth, Tokyo, Japan), a hematoporphyrin derivative,\textsuperscript{20} was intravenously injected, at a dose of 2 mg/kg body weight, 48 h before PDT. After the injection of Photofrin, the patient stayed in a dark room (100–300 luxes of light, shielded by a curtain) for 4 weeks to prevent skin phototoxicity.\textsuperscript{21} Protoporphyrin, uroporphyrin, and conventional blood parameters were monitored before the administration of Photofrin and every week after PDT.

Prior to PDT, a 16- to 18-Fr plastic tube was placed via the trans-hepatic or trans-intestinal route to facilitate endoscopy. The apparatus used was PDT EDL-1 (Hamamatsu Photonics, Hamamatsu, Japan).\textsuperscript{10} A pulse laser by the eximer dye laser with a wavelength of 630 μm (4 millijoules/pulse, 40 Hz) was applied to two or three target lesions through an endoscope to the anastomotic site of the hepaticojejunostomy or occluded tumor lesion, for 10 min. The mean amount of work was 50–100 joules per cm² of surface.\textsuperscript{21} Endoscopic observation and evacuation of debris were performed on days 1, 7, and 28 following PDT. Antibiotic prophylaxis was administered after cholangioscopy.

**Statistical analysis**

Values for continuous variables were expressed as means ± SD. For the univariate analysis, categorical data were analyzed by the $\chi^2$ test. Differences between variables were analyzed by Student’s $t$-test. A two-tailed $P$ value of less than 0.05 was considered significant. Statistical analyses were performed with the computer software Statistica (StatSoft, Tulsa, OK, USA).

**Results**

Of the eight patients, five had extrahepatic bile duct carcinoma, two had intrahepatic cholangiocarcinoma, and one had ampullary carcinoma (Table 1). In six patients, cancer cells were detected in the stump of the bile duct (Table 2). PDT was administered at the anastomotic site of the hepaticojejunostomy in five patients,