Photodiagnosis and Photodynamic Therapy 16 (2016) 110–118

Contents lists available at ScienceDirect

Photodiagnosis and Photodynamic Therapy

journal homepage: www.elsevier.com/locate/pdpdt

Treatment of unresectable extrahepatic cholangiocarcinoma using hematoporphyrin photodynamic therapy: A prospective study

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ARTICLE INFO

Article history:
Received 4 June 2016
Received in revised form
25 September 2016
Accepted 4 October 2016
Available online 5 October 2016

Keywords:
Photodynamic therapy
Cholangiocarcinoma
Efficacy
Safety
Intraductal ultrasonography
Systemic inflammatory response

ABSTRACT

Background: The available evidence of Photodynamic therapy (PDT) combined with stent placement treatment for unresectable extrahepatic cholangiocarcinoma (EHCC) is still insufficient. It also remains unclear whether PDT influences systemic inflammatory response.
Aim: To explore the clinical efficacy and safety of the combination treatment and the systemic inflammatory response in patients with EHCC.
Methods: Patients with unresectable EHCC underwent either the combined treatment using Hematoporphyrin PDT and stent placement (PDT + stent group, n = 12) or stent-only (stent group, n = 27). The primary end-point was overall survival. Tumor necrosis factor (TNF)-α and interleukin (IL)-6 levels were measured. Quality of life was assessed using the Karnofsky performance scale (KPS) every 3 months.
Results: Average survival time (13.8 vs. 9.6 months), and 6-month (91.7% vs. 74.1%), and 1-year (58.3% vs. 3.7%) survival rates of PDT + stent group were significantly increased compared with the stent group. KPS scores in the PDT + stent group were significantly improved. TNF-α and IL-6 levels were significantly increased in the PDT + stent group.
Conclusion: Hematoporphyrin-PDT combined with stent placement is an effective and safe treatment for EHCC. The treatment might promote systemic inflammatory response.

1. Introduction

Cholangiocarcinomas are malignant tumors derived from the epithelial cells of the bile duct and include both intra- and extrahepatic cholangiocarcinomas. The majority of extrahepatic cholangiocarcinomas (EHCC) cannot be diagnosed at early stage because of both their anatomical location and insidious onset. Complete surgical resection (R0) is the preferred curative treatment with a median survival of 22 months and 5-year-survival rates of 30% to 54%. However, the majority of EHCC patients unfortunately present with an advanced and unresectable tumor stage. Only 20% to 30% of patients are ultimate candidates for radical surgery and this proportion is significantly decreased in those with hilar cholangiocarcinomas [1–3]. While radio- and chemotherapies for adjuvant therapy may reduce the tumor load, their efficacy for prolonging survival is not satisfactory and in these cases, the median survival is just 11 months [4]. Palliative treatments such as endoscopic biliary stent placement can alleviate the symptoms of jaundice; however, they have no effect on the overall survival rate with a median survival time of just 6 to 9 months [5–7].

In 1991, McCaughan et al. [8] first reported the use of photodynamic therapy (PDT) in a 57-year-old patient with EHCC. This patient survived for more than 4 years after six sessions of PDT. Since then, an increasing number of clinical studies have shown that a combined approach of PDT with stent placement is a promising treatment option and that patients not only experience significantly longer survival [9] (possibly equivalent to that of surgical R1/R0 resection [10]) but also enjoy an improved quality of life [11]. PDT significantly extends patient survival time when compared to chemotherapy [12]. In addition, PDT could potentially achieve similar survival rates in patients with hilar cholangiocarcinoma as those obtained using surgical R1/R2 resection, even though those patients present with a more advanced clinical tumor stage [13]. It has previously been suggested that PDT could be the preferred palliative treatment approach for unresectable EHCC [14,15]. However, the majority of reports are retrospective studies. Prospective controlled

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http://dx.doi.org/10.1016/j.pdpdt.2016.10.001
1572-1000/

studies have rarely been reported and the available evidence is still insufficient to support this proposition.

Moreover, as EHCC spreads longitudinally, it is difficult to detect accurately the anatomic changes of the bile duct wall after PDT by means of cholangiography. Although cholangioscopy can be used to determine the location and size of the tumor, it is not only technically difficult to operate and financially costly, but also limited in detecting diffuse forms of EHCC that may have spread intramurally. Few assessment methods are available for the objective evaluation of the patient's response after PDT treatment, and as such, there are no standardized recommendations for the time interval between PDT procedures, or the total number of treatments required.

PDT is based on the relatively specific accumulation of photosensitizers in tumor tissues. After intravenous or oral administration, the photosensitizer drug is predominantly concentrated in the tumor tissue and remains inactive. When specific wavelengths of light are delivered to the target cancer site, the photosensitizers are activated by a photochemical reaction to form singlet oxygen and various highly reactive oxygen species that have cytotoxic effects on cellular membranes, mitochondria, endoplasmic reticuli, and the nuclear membranes of tumorous cells [16,17]. Reactive oxygen species can destroy tumor's blood vessels, causing ischemia and subsequent cell death in tumorous tissues [18–20]. In addition, PDT has a significant effect on the immune system [21]. Animal studies have shown that PDT can simultaneously activate a series of intracellular signaling pathways such as those involving Ras, NF-kappaB, extracellular signal regulated kinases (ERK), c-Jun N-terminal Kinase (JNK), and mitogen-activated protein kinase (p38MAPK) [22,23]; as well as triggering the secretion of key inflammatory cytokines such as interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, and so forth, all of which enhance systemic antitumor immunity [24,25]. It remains unclear whether PDT plays a similar role in promoting the systemic inflammatory response in EHCC patients.

Here we present a prospective cohort study on patients with unresectable EHCC who had undergone either a combined approach of PDT with stent placement or stent-only treatment. This study aimed to explore the clinical efficacy and safety of PDT in patients with EHCC, as well as to determine its role on destroying local tumors and enhancing the systemic inflammatory response.

2. Methods

2.1. Study subjects

This was a prospective cohort study. The study population consisted of patients with unresectable EHCC. The criteria for inclusion in this study were as follows: patient age 18–85 years; written and informed patient consent; the use of computed tomography, magnetic resonance cholangiopancreatography, endoscopic ultrasound, and additional examinations for detecting infiltration of tumors into the blood vessels or distant metastasis, thus excluding the possibility of radical resection [26]; and Karnofsky performance scale (KPS) scores ≥50. The following patients were excluded from the study: patients did not provide written and informed patient consent; patients who were undergoing or had previously been treated with radio- or chemotherapies for cholangiocarcinoma; patients with porphyria or hypersensitivity to porphyrins; and pregnant, parturient, or breastfeeding women.

This study was approved by the Ethics Committee of Hangzhou First People's Hospital and conducted in accordance with the Declaration of Helsinki. All patients enrolled in this study signed informed consent documents. Registration of this study on ClinicalTrials.gov (NCT02585856) was postponed until enrolment of the participants had begun.

2.2. Study design

These patients were allocated to a combined treatment of PDT and stent placement (PDT + stent group) or stent-only treatment (stent group) after they had been informed of the efficacy, side effects, and cost of PDT. Patients were followed up by telephone until time of death. Routine blood and liver function tests were conducted preoperatively, as well as 1 and 3 months postoperatively. Levels of TNF-α and IL-6 were determined preoperatively and at 1 week and 1 month postoperatively. Quality of life was assessed using KPS scores every 3 months. Postoperatively, all patients underwent stent replacement by ERCP every 3 to 6 months or when presenting with cholangitis symptoms. The thickness of the tumor mass was routinely measured by intraductal ultrasonography (IDUS) during each ERCP. PDT was repeated in cases of tumor progression when IDUS showed a significant increase in tumor thickness. The incidence of postoperative adverse events and recovery times of the two groups were recorded and compared.

2.3. PDT treatment

2.3.1. Preoperative preparation

Hematoporphyrin (Chongqing huading modern biological pharmaceutical co., LTD Chongqing, China) was used as photosensitizer in this study. First, skin photosensitization testing was performed. An initial volume of 0.1 ml hematoporphyrin was diluted into a 1 ml solution, after which a volume of 0.1 ml was injected intradermally. If systemic urticaria, allergic shock, or swelling or lumps at the local skin site 20 min after injection occurred, this was considered a positive skin photosensitivity test. If these reactions were not experienced and the area at the local skin site was ruddy in color and less than l cm in size, this was considered a negative skin photosensitivity test. Patients with a negative test result received a slow intravenous injection of 2 mg/kg of hematoporphyrin and underwent ERCP and light irradiation 48 h later.

2.3.2. Procedure

Patients were placed in either a prone or lateral position. Cholangiography was performed to identify the main location of the stenosis. IDUS was performed to identify the cholangiocarcinoma lesion and determine its length. As the cylindrical PDT optical fiber could not be passed through the guidewire, an 8.5 Fr. biliary dilation catheter (Soehendra, Wilson-Cook Medical Incorporated, Winston-Salem, US) was inserted into the bile duct via the guide wire and passed through the stenosis. Once the guidewire was removed, the PDT optical fiber (LG-PDT-02 PDT Laser, 400 μm core diameter, 20–50 mm long cylindrical diffuser tip with an X-ray marker on both ends of the diffuser, Chongqing Leigau Medical Devices Co., Ltd., Chongqing, China) was inserted through the dilation catheter and advanced toward the bile duct stenosis point under visual radiography. The dilation catheter was then withdrawn to leave the PDT optical fiber directly across the stricture.

Photoactivation was performed at 640 nm using a diode laser (LG-PDT-02 PDT Laser, Chongqing Leigau Medical Devices Co., Ltd., Chongqing, China) at a light dose of 180 J/cm^2 at power density of 300 mW/cm^2 and irradiation time of 600 s. During the procedure, all patients received pure oxygen via a nasal catheter to enhance the PDT effect. The appropriate length fiber was chosen to span the stricture with an overlap of approximately 5 mm on either side. If tumor length exceeded the maximal diffuser length, an overlap of the fields treated was avoided by a stepwise pull-back of the fiber under X-ray in a proximal to distal fashion. For hilar cholangiocarcinoma (Bismuth III–IV), PDT was performed in selected branches of the left and right hepatic ducts.

In order to avoid light sensitivity and skin damage, patients were required to avoid sun light for 1 week after treatment, as well as