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Review Article

Recent advances of photodynamic therapy for biliary tract cancer

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A B S T R A C T

The prognosis of bile duct cancer (BDC) is limited due to tumor spread along the biliary tree leading to refractory obstructive cholestasis, cholangitis, and liver failure. Palliation with biliary endoprosthesis yields median survival times between 4 and 6 months for advanced BDC. Photodynamic therapy (PDT) is a local photochemical tumor treatment that consists of a photosensitizing agent combined with laser irradiation of a distinct wavelength. Tumor ablation with PDT combined with biliary stenting reduces cholestasis and significantly improves the median survival time. However, the treatment is not widely available, and the photosensitizer used for PDT causes prolonged photosensitivity. Optimal control of tumor spread along the bile ducts and control of cholestasis and cholangitis will prolong survival in 33% to 66% of patients and render them suitable for other antitumor therapies.

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Keywords: Bile duct cancer; Photodynamic therapy; Photosensitizer

Introduction

Bile duct cancer (BDC) is characterized by a slow growth rate and a low propensity for metastasis. However, due to late-onset symptoms, close proximity to important vascular structures in the hilum of the liver, and a tendency to grow into perineural tissue, these tumors are seldom curable at the time of diagnosis.¹ Typically, in unresectable BDC, the only therapeutic strategy is to improve cholestasis via endoscopic or percutaneous drainage or biliary bypass. Although these procedures have no effect on tumor growth and an unclear effect on patient survival, they significantly improve emotional function and ameliorate cholestatic symptoms. The main causes of death in advanced BDC, especially hilar BDC, are liver failure and hepatobiliary infection due to recurrent or refractory cholestasis. Therefore, managing cholestasis is critical for improving the quality of life in patients.² The definitive palliative approach is endoscopic bile duct stenting for the restoration of bile flow. In particular, self-expanding metal stent placement is the current standard treatment for unresectable BDC. However, if stent occlusion occurs, it requires repeated procedures and further stenting. Local control of the tumor prior to stent placement is one option for prolonging stent patency as it prevents tumor advancement into the intrahepatic biliary tree

and may delay fatal complications from progressive jaundice. In addition, the improvement of cholestasis can contribute to maintaining chemotherapy as scheduled and increase survival. Photodynamic therapy (PDT) is a treatment modality for local tumor ablation in BDC. PDT is based on the relatively specific accumulation of photosensitizers, such as porphyrins, in dysplastic or malignant cells. After intravenous, oral, or topical application, the photosensitizing drug predominantly concentrates in tumor tissue and remains inactive until exposed to light of a specific wavelength. When light is delivered to the target cancer site, the photodynamic reaction induces photochemical destruction of tumor tissue mediated by singlet molecular oxygen and other reactive species generated by the reaction between the activated photosensitizer and mucosal oxygen. Damage to tissue occurs via several pathways, including cell necrosis, apoptosis, and ischemia with vascular shutdown;³ in this process, the importance of inflammatory and immune responses has been recognized.⁴

Recently, in a randomized controlled trial, significant survival benefits were observed in patients with unresectable BDC treated with PDT as well as significant improvement in the quality of life after PDT and stenting.⁵

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Rationale for Local Tumor Ablation in Bile Duct Cancer

The tumor biology of BDCs is slightly different from that of other gastrointestinal adenocarcinomas, especially for hilar BDC. In general, the hematogenous spread of hilar BDC is rare; however, nodal metastases may be present in up to one-third of cases.⁶ Extensive subepithelial tumor spread beyond the gross tumor margin is common. The papillary form comprises 10% of all BDCs and the primary form grows as a polypoid intraluminal soft tissue tumor with limited propensity for transmural growth. Tumor multicentricity occurs more frequently in papillary BDC and may be the result of a field change in the biliary epithelium (Fig. 1A). The nodular or polypoid type occurs most commonly in the upper and mid bile duct and is generally present as a fibrotic mass with intraductal projections (Fig. 1B). The sclerosing type comprises 70% of all tumors in the hilum and histologically appears as annular thickening of the bile duct wall with both longitudinal and radial tumor infiltrations (Fig. 1C). Approximately 80% of BDCs, especially perihilar BDCs, are adenocarcinomas that exhibit predominantly longitudinal growth patterns along the biliary tree and most often are highly desmoplastic tumors with infiltration of the adjacent nerve plexus and lymphatics.

In the majority of patients with tumor stenoses, cholestasis can be rapidly relieved by stenting in the distal and middle segments of the bile duct. Independent of the type of stricture, technically successful endoprosthesis placement is possible in 84% to 96% of patients.⁷ Palliative intervention is limited in proximal BDCs. A successful drainage is achieved when bilirubin levels decrease by > 30% to 50%; however, in Bismuth type I and II tumors the bilirubin levels range from 69% to 91%, and in Bismuth type III and IV tumors, they range from 15% to 73%.⁵ Metal stent insertion can improve occlusion rates and reduce the number of therapeutic interventions necessary but does not increase the median survival time. Attempts to affect tumor growth have been made using radiotherapy or chemotherapy. However, randomized prospective studies on the effects of these already long-used additional therapy options have not yet been performed. Several treatment modalities, including PDT and radiofrequency ablation, for local tumor ablation in BDC have been introduced.

Photodynamic Therapy

PDT is a new and promising topical therapy designed to selectively destroy tumor tissues. PDT involves a two-step procedure. A photosensitizer is used, followed by illumination at an appropriate wavelength leading to a photochemical reaction generating cytotoxic singlet oxygen or other oxygen-derived free radicals.^{4,8} These toxic products interact with a number of cellular components, such as microsomes, mitochondria, nuclei, and cell membranes. The initial trigger remains unknown. The selective sensitivity of the tumor microvasculature to PDT may also play an important role. The only relevant side effect of PDT is phototoxicity. The phototoxicity of the most often used hematoporphyrin derivative lasts 4–6 weeks after administration of the drug.

A variety of candidate photosensitizing agents exists for use in PDT based on modifications of porphyrin, chlorine, and chlorophyll. Porphyrin-based photosensitizers, such as hematoporphyrin derivatives and its partly purified commercial preparation, porfimer sodium (Photofrin®; Axcan, Montreal, Quebec), have been the most commonly used sensitizers. Photofrin accumulates in BDC cells with a tumor-to-normal tissue fluorescence ratio of 2:1 at 24 and 48 hours after administration.⁹ Photofrin preferentially accumulates in BDC cells, reaching peak values during the first 2 days, leading to a photochemical reaction, particularly, a type II reaction involving the generation of cytotoxic singlet oxygen or other oxygen-derived free radicals.⁸

These toxic products interact with a number of cellular components like microsomes, mitochondria, nucleus, cell membranes, and so forth. The initial trigger is not yet known. The selective sensitivity of the tumor microvasculature to PDT seems to play an additional important role.¹⁰ The only relevant side effect of PDT is phototoxicity. For the most often used hematoporphyrin derived phototoxicity lasts for 4 to 6 weeks after administration of the drug.¹¹

Fig. 1. Cholangioscopic findings of bile duct cancer (BDC). (A) Papillary type of BDC. Cholangioscopy shows the presence of slightly papillary and mucosal nodularity in the intrahepatic bile duct. In this type of tumor, the mucosal lesion may be minute and detectable only via careful cholangioscopic examination of the entire biliary tree. (B) Nodular or polypoid type of BDC. A polypoid mass partially obstructs the lumen of the common hepatic duct. Mucosal irregularity and intense serpiginous neovascularization are clearly visible on the surface. (C) Sclerosing type of BDC. Cholangioscopy shows luminal narrowing with a whitish mucosal discoloration and neovascularization.

Technical Aspects of Photodynamic Therapy for Bile Duct Cancer

A translucent endoscopic retrograde cholangiogram cannula (with a triple lumen for a guidewire, diffuser, and contrast injection) is inserted into the tumor stenosis, and a 400- μ m-thick quartz fiber with a cylindrical light diffuser and radiopaque markers in the tip (Optiguide DCYL 200 series; QLT Phototherapeutics Inc., Vancouver, BC, Canada) is placed across the tumor stenosis using fluoroscopic guidance. An alternative technique involves a preloaded catheter, which is advanced over a 0.035-inch guidewire proximal to the biliary stricture, using the monorail technique, and positioned into the stricture. The guidewire is then withdrawn, and a diffuser tip with radiopaque markers is positioned across the stricture. However, the peroral transpapillary approach of PDT has some limitations regarding its application and patient follow-up. Furthermore, the flexible-fiber diffusing tip can become ineffective due to fractures caused by bending during peroral cannulation. In comparison, percutaneous cholangioscopy-guided PDT can provide effective, homogeneous irradiation of the targeted lesion with direct visual control. This technique is easily performed and can be monitored repeatedly without periodic peroral endoscopy, similar to the reduced application time and pain associated with the routine exchange of stents during percutaneous transhepatic biliary drainage treatment.¹² The PDT target site is usually temporarily obstructed due to swelling and coagulative necrosis, which can be observed within 1 week following PDT (Fig. 2); therefore, the insertion of an exchangeable plastic endoprosthesis or external drainage tube is necessary.

Photodynamic Effects in Bile Duct Cancer

The tumor-selective enrichment of porfimer has been confirmed in human BDC biopsies using quantitative fluorescence microscopy. BDC cell lines exhibited favorable cellular uptake kinetics for porfimer sodium and excellent phototoxic cell damage responses to PDT *in vitro* and *in vivo* in a human cholangiocarcinoma (CC) xenograft nude mouse model.¹³ Reductions in tumor volume after PDT were assessed *in vivo* after the inoculation of

Buffalo female rats with hepatocellular carcinoma cells.¹⁴ The mean total area of necrosis induced by a single PDT session was 10.2 mm². Histopathological analyses of the surgical specimens revealed that the tumoricidal penetration of PDT with porfimer was limited to a tissue depth of 4 to 4.5-mm.¹⁵ The tumoricidal effect was selective and complete; however, in the deeper layers (5–8 mm from the luminal surface), some viable tumor nests remained in the periductal connective tissue. More current photosensitizers provide deeper tumor penetration and a shorter photosensitivity period. Therefore, the potential indications for PDT in BDC may be as follows: sclerosing tumors without hematogenous metastasis regardless of nodal metastases, superficial spreading of the papillary tumor, residual tumor after resection (R1), prolonged stent patency before insertion, and recanalization of the obstructed stent. Mass-forming intrahepatic CCs, intraductal BDC masses, and hematogenous metastases are not indications for PDT.

Photodynamic Therapy Outcomes for Advanced Bile Duct Cancer

A recent prospective, open-labeled, randomized multicenter study with a group sequential design was conducted to compare the effects between PDT combined with stenting (group A) and stenting alone (group B) in patients with unresectable BDC.⁵ PDT resulted in prolonged survival (group A: median 493 days, $n = 20$; group B: median 98 days, $n = 19$; $P < 0.0001$) and improved biliary drainage and the quality of life. The mean serum bilirubin level decreased from > 10 to 1.8 mg/dL after PDT. The authors concluded that PDT with optimal supportive care improves survival in unresectable BDC patients. The study had to be prematurely terminated because PDT proved superior to simple stenting and further randomization was deemed unethical. The survival benefit associated with PDT was likely due to the amelioration of obstructive cholestasis rather than reduction of the tumor mass. The results of PDT administration in our center were similar to those of a previous study.¹⁶ Twenty patients treated with endoscopic biliary drainage alone (group A) and 27 patients treated with PDT under percutaneous cholangioscopy plus additional percutaneous biliary drainage (group B) were retrospectively analyzed. The mean bilirubin levels decreased significantly in both groups after treatment. The 1-year survival rate was 28% in group A and 52% in group B ($P < 0.05$). The median survival time was 288 days in group A and 558 days in group B ($P = 0.0143$).

The Potential for Photodynamic Therapy As a Neoadjuvant Treatment for Bismuth Type IV Hilar Bile Duct Cancers

PDT has also been applied as neoadjuvant therapy for locally advanced hilar CCs, which are tumors invading both intrahepatic ducts without distant metastasis. In a Bismuth type IV Klatskin tumor case treated with preoperative PDT and surgery in the present study (Fig. 3), the tumor was not suitable for curative resection because it involved both the right and left hepatic ducts. However, distant metastasis was not observed on imaging analyses, including abdominal computed tomography (CT) and magnetic resonance imaging, and only a superficial tumor was noted in the right hepatic duct. Neoadjuvant PDT was performed in the right hepatic duct to preserve the right lobe of the liver. At 1 month following PDT, cholangioscopic biopsy revealed the presence of necrotic tissue in the PDT target site. This patient underwent left hemihepatectomy and hepaticojejunostomy at 6 weeks after PDT. A clear resection margin was reported on the final pathologic examination after surgery. In locally advanced hilar CC, curative

Fig. 2. Cholangioscopic findings before and after photodynamic therapy (PDT). The PDT site is usually obstructed temporarily due to swelling and coagulative necrosis within 7 days after PDT.

Fig. 3. Neoadjuvant photodynamic therapy (PDT) for locally advanced hilar bile duct cancer. (A) Magnetic resonance cholangiopancreatography shows tumors involving the confluence and both the right and left hepatic ducts (arrows). (B, C) Percutaneous cholangioscopy reveals a large papillary tumor in the second branch of the left intrahepatic duct and superficial mucosal nodularity in the proximal part of the right hepatic duct and main duct. (D) Endoscopic evaluation of the effects of PDT at 1 month after treatment in the right hepatic duct. Cholangioscopy shows no viable tumor and only a necrotic surface in the right proximal duct.

resection can be achieved using neoadjuvant PDT.

Another study of neoadjuvant PDT was conducted in seven patients with advanced Bismuth type III and IV carcinomas thought to be unresectable after staging.¹⁵ Following PDT, a curative resection was possible in all patients; 83% were recurrence-free after 1 year, and the 5-year survival rate was 71%. No relevant side effects of PDT occurred except for minor intraoperative phototoxicity in one patient. In the resected specimens, the inner 4-mm layer of the bile duct exhibited complete tumor necrosis without any viable tumor cells. Thus, a tumor necrosis depth of 4-mm may be sufficient for destroying superficial spreading of the tumor to the proximal hepatic duct.

Assessment of Photodynamic Therapy Responses

The evaluation of therapeutic effects of PDT in patients with BDC presents a number of challenges. Ortner et al⁵ evaluated PDT therapeutic effects in advanced BDC cases by comparing the tumor length before and after PDT using the “mother-baby” cholangioscopic technique; however, it has been argued that the authors’ assessment was insufficiently objective. Although the authors reported reduced serum bilirubin levels in the PDT group, plastic biliary endoprotheses were inserted in all patients following the PDT procedure, rendering the assessment of the direct effect of PDT on serum bilirubin difficult. Consequently, the serum bilirubin level may not be the most suitable objective parameter for assessing the responses to PDT. BDCs are characterized by tumor spread along or within the intrahepatic bile ducts, rendering the use of CT to define the responses to PDT based on changes in the tumor mass difficult. Similarly, obtaining objective results when

the evaluation of the PDT response is based solely on the extent to which an occluded bile duct segment has been cleared may also be difficult.¹⁷ Previously, the thickness of the tumor mass before and after PDT treatment was assessed by measuring the thickest part of the tumor before treatment and at every month thereafter.⁸ The mean thickness of the bile duct masses measured using intraductal ultrasonography (IDUS) decreased from 8.7 ± 3.7 mm before PDT to 7.1 ± 2.0 mm ($P = 0.176$), 7.1 ± 2.4 mm ($P = 0.157$), and 5.8 ± 2.0 mm ($P = 0.046$) at 1, 2, and 3 months after PDT, respectively. Therefore, IDUS is useful for evaluating changes in tumor mass thickness following PDT.

Using murine cancer models, Goydos et al¹⁸ showed that serum interleukin (IL)-6 levels were correlated with the tumor burden measured using CT in patients with BDC. At 2 weeks following tumor resection, 3 of 15 patients exhibited decreased IL-6 levels; two had undetectable levels and the third patient had a nearly 10-fold decrease in IL-6 level. Previous results from this center similarly demonstrated significantly reduced IL-6 levels (38.2 ± 9.9 pg/mL; $P = 0.008$) at 1 month after PDT compared with the pretreatment level (282.1 ± 121.8 pg/mL); PDT also decreased the tumor thickness. Conversely, IL-6 levels were unchanged at 1 month following endoscopic retrograde biliary drainage.¹⁹ According to a meta-analysis, the survival time in the PDT group was significantly longer than that in the biliary stenting group, 413 days (95% confidence interval [CI], 349.54–476.54 days) vs 183 days (95% CI, 136.81–230.02 days).²⁰ In addition, changes in the Karnofsky performance level after the procedure indicated good results in the PDT group compared with the biliary stenting group (+6.99 [95% CI, 4.15–9.82] for PDT and –3.93 [95% CI, –8.63–0.77] for biliary stenting). However, there are few ran-

domized prospective studies to date, and most have a relatively small sample size and used different PDT methods and different types of stents. Therefore, a prospective study using a large patient cohort is required to determine whether PDT will help improve overall survival in advanced BDC.

Conclusions

PDT was the only evidence-based endoscopic local therapy other than stenting that enhanced the quality of life in BDC patients. If these results can be supported, the improvement of PDT with the use of new photosensitizers with a greater penetration depth and shorter photosensitivity period or through the administration of better drug treatments and combination therapies to increase tumor necrosis would be warranted.

To continue chemotherapy as scheduled, effective biliary decompression to resolve cholangitis caused by biliary duct obstruction due to BDC must occur first. PDT also improves cholestasis, thus reducing the frequency of cholangitis, which may help prevent a delay in, or the interruption of chemotherapy due to recurrent cholangitis.

Whether radiotherapy and/or chemotherapy further improves the outcome of PDT in patients remains unknown. As such, long-term, randomized multicenter studies are necessary.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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